CLINICAL TRIAL PROTOCOL

Efficacy and Safety of mAnniTol in bowel preparation: assessment of adequacy and presence of Intestinal levelS of hydrogen and methane during elective colonoscopy aFter mAnnitol or standard split 2-liter polyethylene glycol solution plus asCorbaTe – a phase II/III, International, multicentre, randomized, parallel-group, endoscOpist-bliNded, dose-finding/non-inferiority study - SATISFACTION

PROTOCOL NUMBER: Mannitol_03-2018

EudraCT NUMBER: 2019-002856-18

VERSION: 6.0

DATE: 21 JANUARY 2021

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AMENDMENT 1

The purpose of this amendment is to implement the suggestions put forward by the Italian Medicines Agency (AIFA) following review of the original study protocol. The changes to the protocol are as follows:

- The protocol now explicitly states that phase III will begin only once all data collected from phase II necessary for establishing the optimal mannitol dose have been analysed (*Section 4.1.3*).
- *Section 4.1.1* now specifies that should two or all three doses tested in phase II prove to be equally safe and effective, the lowest dose will be selected for phase III of the study.
- To ensure that screening assessments are performed within a time frame such as to properly evaluate patient eligibility and, in particular, that the pregnancy test is performed not more than 7 days prior to the day of colonoscopy, *Section 4.1* and the *schedule of activities* now state that Visit 2 must take place not more than 7 days prior to the day of colonoscopy.
- *Section 5* has been updated to better define the study population.
- *Section 6.4* now indicates permitted and prohibited concomitant medications.
- *Section 9.2* has been added to detail randomization procedures.

The number of sites and Countries involved in the phase II of the study have also been updated.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough red font for deletions and red underline for insertions.

AMENDMENT 2

This amendment was drawn up to align the protocol with the recommendations of the German Federal Institute for Drugs and Medical Devices (BfArM) and has been modified as follows:

- The rationale for the chosen mannitol doses to be tested in the phase II dose-finding study/pharmacokinetic sub-study has been complemented (*Section 2.1* and *Section 4.1.1*). The references reported in *Section 12* have been updated accordingly.
- The reference to Moviprep® Summary of Product Characteristics in *Section 2.2.1* has been updated to its most recent version.
- A schematic diagram of the phase II/III study design has been added in *Section 4.1.*
- The end of study definition has been further articulated (*Section 4.2*).
- The time period for serious adverse event reporting to the sponsor by the investigator has been clarified (*Section 8.3.6*).
- It has been clarified that any urine specific gravity change from the reference normal range will be recorded and managed as an expected adverse event, as the event is to be considered part of the pharmacological profile of mannitol (*Section 2.2.1* and *Section 8.1.4*).

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AMENDMENT 3

This amendment was drawn up to align the protocol with the recommendations of the German Ethics Committee of Mainz and has been modified as follows:

- Exclusion criteria have been implemented to exclude patients with severe acute inflammatory bowel disease and chronically active bowel disease (*Section 1.1* and *Section 5.2*).
- The ability to provide written informed consent has been explicitly mentioned as inclusion criterion (*Section 1.1* and *Section 5.1*).
- In light of a more conservative perspective in terms of patient safety, the stopping rule foreseen in the phase II dose-finding study to limit patient exposure to an ineffective mannitol dose causing repetition of colonoscopy has been revised by reducing from 50% to 25% the failure rate entailing the discontinuation of enrolment (*Section 1.1* and *Section 4.1.1*).

Moreover, the reference to Moviprep® Summary of Product Characteristics in *Section 2.2.1* has been corrected with the reference to the simplified Investigational Medicinal Product Dossier (IMPD) for Moviprep®, in response to a further recommendation of BfArM.

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AMENDMENT 4

The purpose of this amendment is to provide changes and clarifications to the protocol regarding study background information, study assessments and procedures, selection of the dose for phase III, AE reporting and statistical methods.

Accordingly, the protocol has been modified as follows:

- It has been corrected in the *Schedule of Activities* (*Section 1.2*) that the urinalysis at Visit 4 is to be performed 4 hours and 8 hours after the end of study drug self-administration, as stated in the text.
- Additional background information has been added to *Section 2.1* and *Section 2.2*.
- It has been clarified that intestinal gas measurement performed during colonoscopy in each colon segment will be in % Vol for H_2 and % of Lower Explosion Level (LEL) for CH_4 (*Section 1.1*, *Section 3*, *Section 9.4.2*). For the assessment of CH_4 concentration in each colon segment, CH_4 (% LEL) will then be converted in % Vol (*Section 9.4.2*).
- It has been clarified that one of the selection criteria of the dose to be used in the comparative non-inferiority phase (phase III) will be the rate of patients in safe conditions, defined as the absence of potentially dangerous levels of H_2 and CH_4 in each colon segment (*Section 1.1*, *Section 4.1.1*, *Section 9.4.1*).
- It has been clarified that a change of a given parameter is to be considered clinically significant if it causes an additional control or a medical intervention (*Section 1.1*, *Schedule of Activities*, *Section 3*, *Section 4*, *Section 8*, *Section 9.4.2*).
- It has been specified that also systolic and diastolic blood pressure will be monitored during colonoscopy in the comparative non-inferiority phase (phase III), and any clinically significant abnormal finding will be recorded on the eCRF (*Section 1.1*, *Section 1.2.2*, *Section 3*, *Section 4.1.3*, *Section 8.1.3* and *Section 9.4.2*).
- The protocol now explicitly states that CO_2 insufflation and water-aided techniques for colon distension (e.g. water immersion and water exchange) are not allowed during colonoscopy (*Section 1.1* and *Section 4.1*).
- The considerations underlying the stopping rule applied in phase II are described in more detail (*Section 4.1.1*).
- It has been clarified that overnight fasting is required before the dietary restrictions which are to be followed by patients enrolled in the PK sub-study between 24 hours before and the start of mannitol self-administration. Moreover, it has been specified that between 4 and 8 hours after mannitol intake, patients may eat any food which complies with the dietary restrictions, if deemed necessary by the Investigator (*Section 1.1*, *Section 4.1.2*, *Section 6.1.2*).

- It has been clarified that the laboratory and histological results will be available after the completion of the last study procedure on the day of colonoscopy (*Section 4.2*).
- *Section 6.1.2* now specifies that all patients except those enrolled in the PK sub-study should follow dietary recommendations prior to colonoscopy as per local practice at the centre. Moreover, it has been clarified that about half a litre (500 mL) of clear liquid should be drunk after each litre of Moviprep® according to local practice at the centre.
- It has been corrected that a standard urinalysis (not a dipstick urinalysis) will be performed at Visit 2 and Visit 4 (Table in *Section 8.1.4*).
- *Section 8.3.4* now specifies that adverse events should be followed until resolution or stabilization except for those events deemed to be chronic by the Investigator, such as cancer, and that lesions detected during colonoscopy (polyps, adenomas, cancer, etc.) are not to be considered as AEs.
- Clarifications on the calculation of the sample size (*Section 9.1*) and the planned statistical analyses (*Section 1.1*, *Section 9.4.1*, *Section 9.4.3*) have been added.
- The populations for analyses have been updated (*Section 1.1*, *Section 9.3*). Moreover, it has been specified that the safety analyses will be performed both on the Safety Set and on the modified Safety Set by treatment group, with those on the modified Safety set to be considered as supportive (*Section 9.4.2*).
- The publication and data sharing policy (*Section 10.1.10*) has been updated.
- *Section 12* has been updated.

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AMENDMENT 5

With this amendment, minor clarifications have been added to the protocol, as follows:

- The estimated dates of the last patient first visit (LPFV) and the last patient last visit (LPLV) of the study in *Section 1.1* have been updated.
- *Section 1.1*, *Section 1.2.2*, *Section 3*, *Section 4.1.3*, *Section 8.1.3* and *Section 9.4.2* now specify that clinically significant changes of pulse oximetry and heart rate measured during colonoscopy and blood pressure measured immediately prior and after colonoscopy will be recorded. Of note, clinically significant changes of blood pressure measured during colonoscopy will also be reported if considered clinically significant by the Investigator.
- Ranges of the satisfaction scale score and total score of the Bowel Cleansing Impact Review (BOCLIR) to be used at Italian sites only to assess acceptability and tolerability of the bowel preparation have been corrected (*Section 8.1.3*), according to the final validated Italian version of BOCLIR. In particular, the middle 'neutral' option of the satisfaction scale present in the original UK English version was removed as part of the adaptation and validation process in Italian.
- Further examples of lesions detected during colonoscopy that are not to be considered AEs have been added in *Section 8.3.4*.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and all applicable laws and regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and/or Competent Authority, except where necessary to eliminate an immediate hazard to the trial participants. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol and the informed consent form will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any substantial amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented. All changes to the consent form will be IEC/IRB approved.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol number	Mannitol_03-2018
Title of Study	Efficacy and safety of mannitol in bowel preparation: assessment of adequacy and presence of intestinal levels of hydrogen and methane during elective colonoscopy after mannitol or standard split 2-liter polyethylene glycol solution plus ascorbate – a phase II/III, international, multicentre, randomized, parallel-group, endoscopist-blinded, dose-finding/non-inferiority study
Sponsor	NTC S.r.l.
Investigational Sites	Phase II - dose finding: approximately 13 sites located in Italy, Germany and France. Phase II pharmacokinetic sub-study: approximately 5 sites located in Italy. Phase III - non-inferiority: approximately 50 sites located in Italy, Germany, Russia and France.
Study Objectives	**Phase II: Dose-finding/Pharmacokinetic sub-study** o To determine the effective and safe dose of mannitol for adequate bowel cleansing to be used in the comparative non-inferiority phase of the study (phase III). o To define the pharmacokinetic profile of the mannitol doses used in dose finding through a pharmacokinetic sub-study. **Phase III: Non-inferiority** o To demonstrate the non-inferiority of mannitol vs. standard split 2L PEG ASC (Moviprep®) in bowel cleansing for colonoscopy. o To assess the safety and tolerability of mannitol. o To assess the adherence to and acceptability of the bowel preparation with mannitol and Moviprep®.
Study Endpoints	**Phase II - Dose finding** • Primary efficacy endpoint: proportion of patients with adequate bowel cleansing, defined as Boston Bowel Preparation Scale (BBPS) total score ≥6, with a score for each of the three colon segments (right; transverse, including flexures; and left, including sigmoid and rectum) ≥2 during colonoscopy after standard washing and air insufflation for luminal distension. • Secondary efficacy endpoint: caecal intubation rate, defined as the percentage of patients with appendiceal orifice visible to the endoscopist. • Safety and tolerability o Proportion of patients in safe conditions, defined as the absence in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) of potentially dangerous levels of H_2 and/or CH_4 (>4% Vol and >100% of Lower Explosion Level (LEL), which is equal to 5% Vol, respectively) during colonoscopy after standard washing and air insufflation for luminal distension. o Incidence of adverse events from the beginning of study drug self-administration. o Proportion of patients with change from baseline considered clinically significant by the Investigator of haematological and chemical parameters (CBC, creatinine, BUN, eGFR, ALT, AST, glucose, electrolytes) 4 hours and 8 hours after completion of study drug self-administration. o Proportion of patients with change during colonoscopy considered clinically significant by the Investigator of vital signs (heart rate and pulse oximetry).

	Of note, a clinically significant change of a given parameter is defined as a change that causes an additional control or a medical intervention. • Adherence and acceptability o Adherence: study drug completely taken, partially taken, not taken. o Ease of use: numeric rating scale (NRS) (0 = very difficult to 10 = very easy). o Taste: NRS (0 = terrible to 10 = very good). o Willingness to reuse the preparation (yes/no). **Phase II - Pharmacokinetic sub-study** o C_{max}: maximum concentration. o t_{max}: time to maximum concentration. o AUC_0-t_{0-t}: area under concentration-time curve, from 0 to the last blood sampling time point with measurable concentration. o $t_{1/2}$: elimination half-life. **Phase III - Non-inferiority** • Primary efficacy endpoint: proportion of patients with adequate bowel cleansing: BBPS total score ≥ 6, with a score for each of the three colon segments (right; transverse, including flexures; and left, including sigmoid and rectum) ≥ 2 during colonoscopy after standard washing and air insufflation for luminal distension. • Secondary efficacy endpoints o Number, appearance, size, location and histological classification of neoplastic and inflammatory colorectal lesions detected. o Adenoma detection rate, defined as the percentage of patients with at least one adenoma detected. o Caecal intubation rate, defined as the percentage of patients with appendiceal orifice visible to the endoscopist. o Ottawa Scale for bowel cleansing evaluation before washing and air insufflation for luminal distension. • Safety and tolerability o Proportion of patients in safe conditions, defined as the absence in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) of potentially dangerous levels of H_2 and/or CH_4 (>4% Vol and >100% LEL, respectively) during colonoscopy after standard washing and air insufflation for luminal distension. o Incidence of adverse events from the beginning of study drug self-administration. o Proportion of patients with change from baseline considered clinically significant by the Investigator of haematological and chemical parameters 4 hours and 8 hours after completion of study drug self-administration. o Proportion of patients with change from baseline considered clinically significant by the Investigator of vital signs (heart rate, systolic and diastolic blood pressure) measured during visits, as well as clinically significant change of pulse oximetry and heart rate measured during colonoscopy and systolic and diastolic blood pressure measured immediately prior and after colonoscopy. Of note, clinically significant changes of systolic and diastolic blood pressure measured during colonoscopy will also be reported if considered clinically significant by the Investigator. Of note, a clinically significant change of a given parameter is defined as a change that causes an additional control or a medical intervention. • Adherence and acceptability o Adherence: study drug completely taken, partially taken, not taken. o Bowel Cleansing Impact Review (BOCLIR) (only at Italian centres). o Ease of use: NRS (0 = very difficult to 10 = very easy).

	○ Taste: NRS (0 = terrible to 10 = very good). ○ Willingness to reuse the preparation (yes/no).
Study design	This is a phase II/III, international, multicentre, randomized, parallel-group, endoscopist-blinded study that combines a phase II dose-finding study/pharmacokinetic sub-study with a phase III non-inferiority study. **Phase II-dose finding** The parallel-group dose-finding phase will involve 150 patients randomly assigned (1:1:1 ratio) to one of the following three treatment groups: • 50 g mannitol powder to be dissolved in 500 ml of water • 100 g mannitol powder to be dissolved in 750 ml of water • 150 g mannitol powder to be dissolved in 1000 ml of water Randomization is stratified by centre and by the presence of constipation (yes/no), defined as the recurrent use of laxatives or Bristol Stool Form Scale (BSFS) <3 in the two weeks before randomisation. To limit patient exposure to an ineffective dose causing repetition of colonoscopy, the adequacy of bowel cleansing will be monitored continuously and enrolment in a treatment group will be discontinued as soon as 25% of treated patients present inadequate bowel cleansing causing repetition of colonoscopy. The stopping rule will be applied in each treatment group as follows: • Up to the 25th enrolled patient, enrolment in a treatment group will be stopped as soon as 6 patients present inadequate bowel cleansing causing repetition of colonoscopy. • From the 26th enrolled patient on (if treatment was not discontinued earlier), enrolment will be stopped as soon as 25% of the patients present inadequate bowel cleansing causing repetition of colonoscopy. The appropriate mannitol dose to be used in phase III will be singled out based on the following criteria: • 75% or greater rate of adequate bowel cleansing, defined as BBPS total score ≥6, with a score for each of the three colon segments (right; transverse, including flexures; and left, including sigmoid and rectum) ≥2 during colonoscopy after standard washing and air insufflation for luminal distension. • Rate of patients in safe conditions defined as the absence of potentially dangerous levels of H_2 and CH_4 in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension). • Clinical judgment based on the caecal intubation rate, the incidence of adverse events, treatment adherence and acceptability (ease of use, taste and willingness to reuse the preparation). Should two or all three doses prove to be equally safe and effective, the lowest dose will be selected for phase III of the study. **Phase II-Pharmacokinetic sub-study** A single-group design for each mannitol dose will be implemented. Mannitol is contained in foods in a certain amount. To minimize the error of measuring mannitol plasma concentration after the intake of the investigational drug, dietary restrictions are required, after overnight fasting, between 24 hours before and the start of drug self-administration, while fasting is required afterwards up to 8 hours after mannitol intake. Of note, between 4 and 8 hours after mannitol intake, patients may eat any food which complies with the dietary restrictions based on the INRAN tables, if deemed necessary by the Investigator. Venous blood samples will be drawn from a sub-group of at least 10 patients in each dose group at the following times:

	• T_0 (baseline before mannitol self-administration) • T_1 (1 hour ± 5 min after completion of mannitol self-administration) • T_2 (2 hours ± 5 min after completion of mannitol self-administration) • T_4 (4 hours ± 10 min after completion of mannitol self-administration, before colonoscopy) • T_8 (8 hours ± 10 min after completion of mannitol self-administration, after colonoscopy) If patients do not undergo all PK evaluations, the sub-study sample size will be increased to guarantee at least 8 PK evaluations for each assessment time. **Phase III-Non-inferiority** A parallel-group design will be implemented to test the non-inferiority of bowel cleansing with the mannitol dose selected in phase II against standard split 2L PEG ASC. Phase III will begin only once all data collected from phase II necessary for establishing the optimal mannitol dose have been analysed. The non-inferiority study will involve 696 subjects randomized in a 1:1 ratio to one of the two cleansing agents. Randomization is stratified by centre. **Study visits** In both phases, the study will consist of four visits: Visit 1 (≤ 28 days before the day of colonoscopy): after signed written informed consent is obtained from the patient, information concerning demographics, medical history, concomitant medications and indications for colonoscopy will be collected in the electronic case report form (eCRF). Visit 2 (≤ 7 days before the day of colonoscopy): to complete the verification of inclusion/exclusion criteria, a blood sample will be drawn to assess the haematological and chemical parameters of all patients and to perform a pregnancy test for women of childbearing potential. Assessments include a urinalysis and the measurement of vital signs (heart rate and blood pressure). Visit 3 (≤ 7 days before the day of colonoscopy): if eligibility criteria are met, the BSFS will be administered (only in phase II), randomization will be performed, study drug will be dispensed and verbal and written instructions for its use will be provided. Patients will be given a form on which to indicate date and time of start and end of study drug self-administration. More than one visit may take place on the same day. Visit 4 (day of colonoscopy): • <u>Phase II - dose finding</u> A blood and urine sample will be collected 4 hours ± 30 minutes and 8 hours ± 30 minutes after the end of study drug self-administration. After completion of bowel preparation and prior to colonoscopy, patients will complete the questionnaires on the acceptability of and adherence to the study drug to which they were assigned. The blinded endoscopist will then perform the scheduled colonoscopy using a standard colonoscope recording data on bowel cleansing using the BBPS and measuring intestinal gas (H_2, CH_4 and O_2) concentrations. The endoscopist will also confirm caecal intubation, defined as identification of the appendiceal orifice. Drugs administered for the procedure will be recorded. Vital signs (heart rate and blood pressure) will be measured prior to colonoscopy. Oxygen saturation and heart rate will be measured continuously during colonoscopy, but only clinically significant abnormal findings will be recorded on the eCRF, where clinically significant means that these abnormal findings cause an additional control or a medical intervention. The incidence of adverse events will be recorded.

	• Phase II - pharmacokinetic sub-study Patients participating in the pharmacokinetic sub-study will sign a separate informed consent form. Venous blood samples will be drawn at the time points mentioned previously and analysed at a centralized bioanalytical laboratory only for the determination of mannitol concentrations. • Phase III - non-inferiority Along with the assessments described for phase II (dose finding), the following additional assessments will be performed: o H_2, CH_4 and O_2 levels will be measured following the introduction of the colonoscope in the sigmoidal-rectum junction (15-25 cm from anal margin) before standard washing and air insufflation. o Number, appearance, size location and histological classification of neoplastic and inflammatory colorectal lesions detected. o Ottawa Scale for bowel cleansing evaluation before washing and air insufflation for luminal distension. o Bowel Cleansing Impact Review (BOCLIR) (at Italian centres only). In both phases, the study drugs will not be blinded, but all endoscopists will not be aware of group allocation; patients and site personnel involved in the randomization of the patient and management of the study drugs will be instructed not to disclose group allocation to the endoscopists.
Number of Patients	The study population is made up of 846 adult patients scheduled for elective (screening, surveillance or diagnostic) colonoscopy; 50 patients in each of the three mannitol dose groups for phase II, and 348 patients in each of the two treatment groups for phase III.
Inclusion Criteria	1. Ability of patient to consent and provide signed written informed consent 2. Age ≥ 18 years 3. Males and females scheduled for elective (screening, surveillance or diagnostic) colonoscopy to be prepared and performed according to the European Society of Gastrointestinal Endoscopy (ESGE) Guideline 4. Patients willing and able to complete the entire study and to comply with instructions
Exclusion Criteria	1. Pregnancy or breastfeeding. Females of childbearing potential must have a negative pregnancy test at Visit 2 and must practice one of the following methods of birth control throughout the study period (unless postmenopausal or surgically sterile, or whose sole sexual partner has had a successful vasectomy): oral, implantable, or injectable contraceptives (for a minimum of three months before study entry) in combination with a condom; intrauterine device in combination with a condom; double barrier method (condom and occlusive cap with spermicidal foam/gel/film/cream/suppository). 2. Severe renal failure: glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 estimated by means of simplified MDRD equation. 3. Severe heart failure: NYHA Class III-IV. 4. Severe anaemia (Hb ≤ 8 g/dl). 5. Severe acute and chronically active Inflammatory Bowel Disease; patients in clinical remission (Crohn's Disease Activity Index - CDAI < 150 for Crohn Disease and Partial Mayo Score ≤ 2 for Ulcerative Colitis) are allowed. 6. Chronic liver disease Child-Pugh class B or C. 7. Electrolyte disturbances (Na, Cl, K, Ca or P out of normal ranges). 8. Recent (< 6 months) symptomatic acute ischemic heart disease. 9. History of significant gastrointestinal surgeries, including colon resection, sub-total colectomy, abdominoperineal resection, de-functioning colostomy or ileostomy, Hartmann's procedure and other surgeries involving the structure and function of the colon.

	10. Use of laxatives, colon motility altering drugs and/or other substances (e.g. simethicone) that can affect bowel cleansing or visibility during colonoscopy within 24 hours prior to colonoscopy. 11. Suspected bowel obstruction or perforation. 12. Indication for partial colonoscopy. 13. Patients who have received an investigational drug or therapy within 5 half-lives of the first visit. 14. Patients previously screened for participation in this study. 15. Hypersensitivity to the active ingredients or to any of the excipients of the study drugs. 16. Contraindication to Moviprep® (only for phase III).
Study Products	• Test (phase II and phase III): mannitol solution (Pearlitol® PF) • Standard: (phase III): 2L PEG ASC (Moviprep®)
Key Study Procedures	A schedule of assessments is available in *Section 1.2* The main assessments of the study are as follows: • Evaluation of bowel preparation The Boston Bowel Preparation Scale (BBPS) uses a four-point scoring system applied to each of the three segments of the colon. Each segment is scored from 0 to 3, with total score ranging from 0 to 9. • Measurement of intestinal H_2, CH_4 and O_2 concentrations Intestinal H_2, CH_4 and O_2 concentrations will be measured in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension using a multi-gas detector (Dräger X-am® 8000). Of note, CO_2 insufflation and water-aided techniques for colon distension (e.g. water immersion and water exchange) will not be allowed. The gas detector has no direct contact with the patient's body but is connected through a one-way pump and a filter to a polyvinyl catheter inserted into the working channel of the colonoscope. The intestinal gases are conveyed to the gas detector by a one-way pump that prevents the return of gases to the colonoscope. Use of any electrocautery device is allowed only during withdrawal and after washing and air insufflation. If H_2 and/or CH_4 levels are potentially dangerous, any electrosurgical procedure must be avoided. In phase III only, intestinal H_2, CH_4 and O_2 will be measured following the introduction of the colonoscope in the sigmoidal-rectum junction (15-25 cm from anal margin) before standard washing and air insufflation. • Blood sampling for pharmacokinetics Patients participating in the pharmacokinetic sub-study will have blood draws before mannitol self-administration (T_0), and 1 hour (T_1), 2 hours (T_2), 4 hours (T_4) and 8 hours (T_8) after completion of mannitol self-administration. • Safety The assessment of overall safety consists in recording and evaluating all adverse events, haematological and chemical parameters, and vital signs.
Statistical considerations	**Populations for analyses** The following populations will be used for the statistical analyses: • Safety set: all patients who take the study preparation, even only partially. • Modified Safety set: all patients who take the study preparation, even only partially, and who do not meet significant protocol violations that regard inclusion/exclusion criteria. • PK population (only for the pharmacokinetic sub-study): all randomized patients who complete the mannitol treatment and have at least one PK assessment, regardless of the outcome of colonoscopy.

	• Full Analysis Set (FAS): all randomized patients who take the study preparation, even only partially, undergo colonoscopy, and have a BBPS available for at least one colon segment after standard washing and air insufflation for luminal distension. • Per protocol (PP): all randomized patients who meet the following criteria: o Treatment with the study drug completed. o Colonoscopy completed adequately in the absence of pathological obstruction that prevents reaching the right colon, including cecum, (i.e. endoscope does not find obstacles other than faecal material), and without acute deterioration of general conditions causing the suspension of the procedure. o BBPS and H_2 and CH_4 measurement are available for all colon segments after standard washing and air insufflation for luminal distension. o No significant protocol violations that regard inclusion/exclusion criteria or that can impact evaluations. **Analysis of primary variables** **Phase II – dose finding** The identification of the effective and safe mannitol dose to be used in the non-inferiority assessment will be performed at the end of dose finding based on the following criteria: • 75% or greater rate of adequate bowel cleansing defined as BBPS total score ≥6, with a score for each of the three colon segments (right; transverse, including flexures; and left, including sigmoid and rectum) ≥2 during colonoscopy after standard washing and air insufflation for luminal distension. • Rate of patients in safe conditions defined as the absence of potentially dangerous levels of H_2 and CH_4. • Clinical judgment based on the caecal intubation rate, the incidence of clinically significant adverse events, treatment adherence and acceptability. Descriptive statistics and 95% CI of the proportion of patients with adequate bowel cleansing will be provided for each dose. Logistic regression models will be applied to assess the influence of the two stratification factors and other potential prognostic factors on dose response. No between-group comparisons will be performed. The decision will be made on the basis of descriptive statistics and 95% CIs. **Phase III – non-inferiority** The proportion of patients with adequate bowel cleansing (BBPS total score ≥6, score ≥2 for each segment) will be calculated to evaluate the non-inferiority of the test drug vs the standard drug. Non-inferiority will be assessed by computing the two-tailed 95% confidence interval (CI) of the difference between the two proportions $\pi T - \pi S$. Non-inferiority is met if the 95% CI does not cross the predefined non-inferiority margin $\Delta = -0.08$ and lies entirely to the right of the margin. Furthermore, if the 95% CI lies entirely to the right of 0, it will be possible to claim for the superiority of the mannitol solution (Pearlitol® PF). The non-inferiority margin $\pi T - \pi S = -0.08$ corresponds to a relative risk $\pi T/\pi S = 0.906$ when the proportion of successes in the standard group is 0.85. Should the proportion of successes in the standard group be lower than 0.85, the non-inferiority margin will be adjusted in order to have a relative risk of at least 0.906. The analysis will be performed on both the FAS and PP populations. Results from the two populations will have equal importance.
Duration of the study	Estimated date of the first visit of the first patient (FPFV): 15/03/2020 Estimated date of the first visit of the last patient (LPFV): 01/09/2021 Estimated date of the last visit of the last patient (LPLV): 29/09/2021
Participant Duration	The duration of the study for each patient is variable and depends on the time elapsing between the pre-colonoscopy visits and scheduled colonoscopy but should not be longer than 28 days.

Version and date	V6.0, 21 January 2021

1.2 SCHEDULE OF ACTIVITIES (SOA)

1.2.1 PHASE II – DOSE FINDING/PHARMACOKINETIC SUB-STUDY

Visit	Pre-colonoscopy period[1]			Day of colonoscopy V4
	V1 (≤ 28 days before V4)	**V2 (≤ 7 days before V4)**	**V3 (≤ 7 days before V4)**	
Written informed consent	X			
Demographics, medical history, indication for colonoscopy	X			
Concomitant medications	X	X	X	X
Drugs used for colonoscopy				X
Blood sampling for standard haematology, clinical chemistry and electrolyte levels		X		X[2]
Urinalysis		X		X[2]
Vital signs		X[3]		X[3]
Pulse oximetry and heart rate				X[4]
Pregnancy test		X[5]		
Inclusion/exclusion criteria verification			X	
Bristol Stool Form Scale			X	
Randomization			X	
Dispensation of study drug and instructions			X	
Questionnaires on adherence and acceptability				X[6]
Blood sampling for pharmacokinetic sub-study				X[7]
Colonoscopy				X
Measurements of intestinal gas concentrations				X
Boston Bowel Preparation Scale				X
Confirmation of caecal intubation				X

Adverse events[8]	X	X	X	X

[1] More than one visit may take place on the same day.
[2]4 hours and 8 hours after end of study drug self-administration.
[3]Heart rate, diastolic and systolic blood pressure at Visit 2 and at Visit 4 prior to colonoscopy.
[4] Only clinically significant abnormal oxygen saturation and heart rate values obtained during colonoscopy are to be recorded on the eCRF, where clinically significant means that these abnormal finding cause an additional control or a medical intervention.
[5]A blood beta hCG pregnancy test is required for women of childbearing potential.
[6]4 hours after end of study drug self-administration, before colonoscopy.
[7]Only for patients who signed the separate informed consent form for the pharmacokinetic sub-study. Before mannitol self-administration (T_0 - baseline), and 1 hour (T_1), 2 hours (T_2), 4 hours (T_4) and 8 hours (T_8) after completion of mannitol self-administration.
[8]Adverse events are to be collected from signature of the informed consent form up to and including the day of colonoscopy.

1.2.2 PHASE III – NON-INFERIORITY

Visit	Pre-colonoscopy period[1]			Day of colonoscopy V4
	V1 (≤ 28 days before V4)	V2 (≤ 7 days before V4)	V3 (≤ 7 days before V4)	
Written informed consent	X			
Demographics, medical history, indication for colonoscopy	X			
Concomitant medications	X	X	X	X
Drugs used for colonoscopy				X
Blood sampling for standard haematology, clinical chemistry and electrolyte levels		X		X[2]
Urinalysis		X		X[2]
Vital signs		X[3]		X[3]
Pulse oximetry, diastolic and systolic blood pressure and heart rate				X[4]
Pregnancy test		X[5]		
Inclusion/exclusion criteria verification			X	
Randomization			X	
Dispensation of study drug and instructions			X	
Questionnaire on adherence and acceptability				X[6]
Bowel Cleansing Impact Review				X[7]
Colonoscopy				X
Measurements of intestinal gas concentrations				X
Boston Bowel Preparation Scale				X
Ottawa Scale				X
Detection of colorectal lesions				X
Confirmation of caecal intubation				X
Adverse events[8]	X	X	X	X

[1] More than one visit may take place on the same day.
[2] 4 hours and 8 hours after end of study drug self-administration.
[3] Heart rate, diastolic and systolic blood pressure at Visit 2 and Visit 4 prior to colonoscopy.
[4] Only clinically significant abnormal oxygen saturation and heart rate values obtained during colonoscopy and diastolic and systolic blood pressure values measured immediately prior and after colonoscopy are to be recorded on the eCRF, where clinically significant means that these abnormal finding cause an additional control or a medical intervention. Of note, clinically significant changes of diastolic and systolic blood pressure measured during colonoscopy will also be reported if considered clinically significant by the Investigator.
[5] A blood beta hCG pregnancy test is required for women of childbearing potential.
[6] 4 hours after end of study drug self-administration, before colonoscopy.
[7] Only for Italian centres. 4 hours after end of study drug self-administration, before colonoscopy.
[8] Adverse events are to be collected from signature of the informed consent form up to and including the day of colonoscopy.

2 INTRODUCTION

2.1 OVERVIEW

Effective colorectal screening relies on colonoscopy, the current standard method for imaging the mucosa of the entire colon. The diagnostic accuracy of colonoscopy depends largely on the quality of colonic cleansing. Large-scale reviews have shown rates of incomplete colonoscopy, defined as the inability to achieve caecal intubation and mucosal visualization effectively, to be between 10% and 20%, well over the targets recommended by the U.S. Multi-Society Task Force on Colorectal Cancer (*Salzmann et al., 2015*). Inadequate bowel cleansing can lead to missed lesions, increased complications, unnecessarily prolonged examinations and additional patient discomfort (*Parra-Blanco et al., 2014*).

Wong et al. conducted a study on 5470 colon rectal cancer (CRC) screening patients aimed at evaluating the factors independently associated with the quality of bowel preparation. Poorer bowel preparation quality was associated with longer caecal intubation time and longer colonoscopy withdrawal time (both $P<0.001$). The detection of colorectal neoplasia and advanced neoplasia was used as the outcome measure controlling for the recognized risk factors of CRC. Compared with subjects with excellent bowel preparation, those with good (AOR=0.354, 95% CI 0.270–0.464, $P<0.001$) and fair or poor (AOR=0.406, 95% CI 0.303–0.545, $P<0.001$) bowel cleansing were significantly less likely to have colorectal neoplasia detected. The same applied to colorectal advanced neoplasia and neoplastic lesions sized ≥5 mm in diameter (*Wong et al., 2016*).

The European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study was a prospective observational study of 5832 patients conducted at 21 centers from 11 countries. The detection of polyps of any size depended on cleansing quality: odds ratio (OR) 1.73: 95% confidence interval (CI)[1.28, 2.36] for intermediate-quality compared with low-quality preparation; and OR 1.46: 95% CI[1.11, 1.93] for high-quality compared with low-quality preparation. For polyps >10 mm in size, corresponding ORs were 1.0 for low-quality cleansing, OR 1.83: 95% CI[1.11, 3.05] for intermediate-quality cleansing, and OR 1.72: 95% CI[1.11, 2.67] for high-quality cleansing. The authors concluded that cleansing quality critically determines quality, difficulty, speed, and completeness of colonoscopy (*Froehlich et al., 2005*).

Rex et al. conducted a study aimed at measuring the impact of bowel preparation on total direct cost as well as procedure time and volume. For 200 consecutive outpatient colonoscopies in persons with intact colons both at a private university hospital and at a public university hospital, the authors recorded the time spent suctioning fluid and feces from the colon and the time spent washing the colon to clean the mucosa. The endoscopist were asked to designate examinations that should be repeated at an interval sooner than would otherwise be recommended because of imperfect preparation. Suctioning fluid and washing occupied 6% and 1.5% of total examination time (including insertion and withdrawal) at the public hospital and 9% and 1.3% at the private

hospital. Patients at the public hospital were more likely to have an aborted examination (6.5% vs 1%, p = 0.004) and to be brought back earlier than suggested or required by current practice standards because of imperfect bowel preparation (20% vs 12.5%, p = 0.04). Cost analysis indicated that to complete the initial examinations and the first round of surveillance, imperfect bowel preparation resulted in a 12% increase in costs at the university hospital and a 22% increase at the public hospital (*Rex et al., 2002*).

Two single-center studies quantifying adenoma miss rates based on repeated colonoscopies done shortly after sub-optimally prepared examinations yielded similar results with overall adenoma miss rates reported as 42% and 47%. On a per-patient basis, at least one adenoma was missed in 25% and 34% of these two cohorts. The miss rate for advanced lesions (previously quantified as 0–7% in tandem colonoscopy studies) was 27% in one study, with the other study reporting 18% for missed lesions that if identified would have changed the surveillance schedule (*Lebwohl et al., 2013; Lebwohl et al., 2011; Chokshi et al., 2012*).

In Europe, the most commonly used preparations for colonoscopy are osmotic laxatives, represented in most cases by polyethylene glycol (PEG). PEG-based cleansing agents are available in 4 L (high volume) or 2 L (low volume) formulations and are to be taken either on the same day or split between 2 days (split-dose regimen). Currently, the split dose 4L PEG-ELS preparation (PEG with electrolytes) is considered to deliver the highest quality for colon preparation (*Hassan et al., 2013, Bechtold et al., 2016, Salzmann et al., 2015*). However, 15% of patients self-administering PEG-ELS find it intolerable due to its unpleasant taste, large volume or nausea (*Marshall et al., 1993*). Therefore, other preparations have been conceived to reduce the drawbacks associated with PEG-ELS.

Sodium phosphate preparations are hyperosmotic cleansing agents given as an alternative to PEG because of the smaller volume required, and consequently better patient compliance (*Markowitz et al., 2009*). However, the use of sodium phosphate solutions has raised concerns regarding phosphate-induced renal disease (*FDA safety alert, 2006*) and the European Society of Gastrointestinal Endoscopy (ESGE) guidelines no longer recommend the routine use of sodium phosphate (*Hassan et al., 2013*).

The newest agent in the hyperosmotic category is a combination of sodium picosulfate and magnesium oxide in a low volume preparation (approximately 2 L). Efficacy in terms of bowel cleansing is comparable to sodium phosphate and PEG-ELS (*Renault et al., 2008, Katz et al., 2013*). However, due to reported electrolyte abnormalities in the elderly, sodium picosulfate should be used with great caution in this population and should be avoided in patients with renal insufficiency (*Bechtold et al., 2016*).

Not only the volume of administered fluid, but also the timing of preparation is reported to have a significant impact on the quality of bowel preparation. Giving part of the bowel preparation on the

same day as the colonoscopy was reported to result in higher-quality colonoscopy compared with the ingestion of the entire preparation on the day or evening before colonoscopy (*Salzmann, 2010*).

In study evaluating the efficacy and tolerability of a split-dose PGE-ELS plus bisacodyl and a regular diet, 187 patients were randomly assigned to receive either 3 L of PGE-ELS (n = 96; Group A) with a liquid diet on the day before colonoscopy, or 2 L of PGE-ELS, one tablet of bisacodyl, and a minimally restricted diet on the day before colonoscopy, and then 1 L of the same solution on the day of colonoscopy (n = 91; Group B). Colon cleansing was significantly better in Group B with regard to the overall quality of the preparation ($p < 0.05$). Compliance was significantly higher in Group B as evidenced by the lower number of patients who discontinued the preparation (4 vs. 15; $p = 0.02$) because of side effects such as nausea or vomiting. The degree of discomfort, adverse events, and willingness to retake the preparation were not significantly different between the groups. The authors concluded that colonic preparation with split-dose polyethylene glycol-electrolyte provided better quality colon cleansing and higher compliance, with less dietary restrictions, than preparation with whole-dose polyethylene glycol-electrolyte (*El Sayed et al., 2003*).

In a single-blind, active control, randomized study of 895 patients, Marmo et al. evaluated the degree of colon cleansing comparing split-dosage versus non-split-dosage of two different PEG volumes (low-volume PEG + ascorbic acid vs standard-volume PEG-electrolyte solution). Overall compliance was excellent (97%) for both preparation methods. PEG plus ascorbic acid produced the same degree of cleansing as standard-volume PEG-electrolyte solution (77% vs 73.4%, respectively, within the split-dosage group and 41.7% vs 44.3%, respectively, within the non-split-dosage group). Independently of PEG volumes, the split-dosage regimen produced markedly superior cleansing results over the same-day method (good/excellent 327/435, 75.2% vs 186/433, 43.0%, $P = .00001$). The degree of bowel cleansing affected both caecal intubation (failed intubation 11.7% with fair/poor preparation vs 1.2% with good/excellent preparation, $P = .00001$) and polyp detection rates (12.2% with fair/poor vs 24.6% with good/excellent preparation, $P = .001$). Aborted procedures were significantly more frequent in the non-split-dosage arm (21.2% vs 6.9%, odds ratio [OR] 3.60 [2.29-5.77], $P < .0001$ (*Marmo et al., 2010*).

The ideal method of bowel preparation for colonoscopy is thus one that provides a combination of effectiveness, safety, ease of self-administration, low cost and good patient acceptance. While the current available preparations offer effectiveness and safety at a reasonable level, up to 20%-25% of all colonoscopies are reported to have inadequate bowel preparation (*Johnson et al., 2014*) and patient acceptance is still an issue.

Mannitol is a sugar alcohol only partly absorbed following oral administration. It acts as an osmotic laxative by increasing osmolarity in the gut and consequently the amount of fluid that is retained in the bowel and excreted. Mannitol was widely used in the late ‘70s and early ‘80s as a bowel cleansing prep agent for colonoscopy thanks to its effectiveness, ease of self-administration related

to reduced volumes, high patient acceptance and lack of significant systemic side effects. Eleven clinical studies investigating the safety and efficacy of mannitol as a bowel cleansing agent were published between 1980 and 2018. All published studies used doses of mannitol between 50 g and 150 g, always given in a single dose. Mannitol at the dose of 50 g showed some effectiveness as bowel cleansing agent: 18 out of 21 patients treated with mannitol combined with saline irrigation showed a good cleansing outcome compared with saline alone (11 out of 21) or mannitol alone (12 out of 20) (*Minervini et al., 1980*), and 17 out of 19 patients treated with mannitol alone had a satisfactory or excellent result (*Gilmore et al., 1981*). Mannitol at 100 g showed comparable efficacy results to several bowel cleansing agents, including sodium phosphate, 4 L and 2 L PEG, and substantially presented a similar incidence of adverse events (*Macedo et al., 2003*; *Miki et al., 2008*; *Mendoza et al., 2008*; *Viera et al., 2012*; *Kaiser-Júnior et al., 2018*). At the dose of 150 g, mannitol was as effective as sodium picosulfate with a similar safety profile (*Müller et al., 2007*). In summary, 533 patients were treated with mannitol in comparative trials and its efficacy was found to be comparable to that of the comparators; most bowel preparations were at least adequate, with the number of excellent or good preparations ranging from 66% to 90% and very few poor or unsatisfactory results (see *Investigator's Brochure* for more details).

Currently, mannitol is commonly used in Brazil, although off-label, where it is still the most popular formulation for bowel cleansing. In Europe and the US, mannitol is currently not used for bowel cleansing due to some cases of intestinal explosion (one lethal) that, despite the absence of controlled clinical trials, have been attributed to the presence of a mixture of methane, hydrogen and oxygen during the execution of diathermy-electrocautery after biopsy. A systematic review of the medical research published from 1952 to 2006 was conducted by Ladas et al. (2007). A total of 20 cases of colonic gas explosion were identified, 14 of which had been preceded by bowel preparation with mannitol and sorbitol (*Josemanders et al., 2006*). Due to these reported cases of intestinal explosion after the use of diathermy-electrocautery during colonoscopy in patients treated with mannitol for bowel preparation, the use of mannitol for bowel cleansing has been limited as summarized in the guidelines of the ESGE, which state: "*Mannitol has also been used for bowel preparation; it seems to be as effective and as well tolerated as OSP (NaP) or PEG. However, its use has almost been abandoned because of the explosion risk when diathermy is used during colonoscopy*" (*Hassan et al., 2013*).

Notably, at the time when the cases of intestinal explosion were reported, mannitol was one of the most commonly used laxatives, since others such as PEG had not yet been developed. Furthermore, routine techniques performed nowadays during colonoscopy such as air insufflation, suction and washing most likely remove residual gases, if present, or reduce their concentrations below those associated with the risk of intestinal explosion (*Macedo et al., 2003, Avgerinos 1984*).

Recent scientific literature indicate that safety problems reported in the past do not seem to be an issue in regions where mannitol is used for this indication. Currently available scientific data indicate that the baseline concentration of CH_4 in the bowel is not only related to the type of

laxative used but is also attributable to other factors such as bowel flora, constipation, sorbitol malabsorption, and prior antibiotic use (*Ladas et al., 2007*, *Attaluri et al. 2010*, *Corazza et al. 1988*). Individuals can be categorized as methane producers and non-producers, about 35% and 65% of the healthy western population respectively (*Bond et al., 1971*), regardless of the method of intestinal preparation. Recently, methane production has been also linked to intestinal transit time (*Triantafyllou et al., 2014*).

Hydrogen and methane are produced by fermentation of non-absorbable (e.g. lactulose, mannitol) or incompletely absorbed carbohydrates (e.g. lactose, fructose, sorbitol) by the colonic flora and are potentially dangerous at levels ≥ 4% Vol (H_2) and ≥ 5% Vol (CH_4), in presence of an O_2 concentration ≥ 5% Vol. The production of H_2 is affected by dietary intake and the period of fasting prior to measurement, whereas the production of CH_4 is unrelated to diet.

Potentially dangerous concentrations of H_2 and/or CH_4 may be present even with the most commonly used bowel preparation methods, particularly also in patients prepared with PEG, as demonstrated by the study of Gallagher (*Gallagher et al. 1992*). The aim of this study was to compare intracolonic gas compositions after administration of PEG and mannitol preparations for full colonoscopy and phosphate enema for left-sided colonoscopy. Its purpose was to establish if explosion is still a potential occurrence after preparations with PEG, that does not interact with colonic bacteria. Patients were prepared whit PEG (N=23), phosphate enema (N=34) and mannitol (N=4). Air insufflation was used in all procedures. High concentrations of hydrogen were detected in 3 out of 38 gas samples in the PEG group, in 2 of 41 samples in the phosphate enema group and in one of the 8 samples in the mannitol group. All patients had a coexisting intracolonic oxygen concentration > 5%. The results of this study proved that potentially dangerous concentrations of hydrogen may occur even with the currently most used preparations. Therefore, for the new preparations it is relevant to compare the proportion of patients who may have potentially dangerous H_2 and/or CH_4 levels with the preparations currently in use.

To address any remaining concerns related to a more frequent accumulation of colonic gas to potentially dangerous levels following bowel preparation with mannitol, this study will be conducted with particular attention on safe bowel preparation, comparing the proportion of patients without potentially dangerous levels of H_2 and CH_4 after preparation with mannitol and PEG.

The purpose of this dose finding/comparative efficacy study is to first single out the most appropriate dose of mannitol for bowel preparation and, subsequently, demonstrate the non-inferiority of the efficacy of mannitol vs standard split 2L PEG ASC (Moviprep®) in bowel preparation for colonoscopy. The selected doses of mannitol to be investigated in the dose finding/ comparative efficacy study are 50 g, 100 g and 150 g, since this range includes the minimum and maximum mannitol doses used effectively in the proposed indication, as reported in published literature. The study includes a pharmacokinetic sub-study to define the pharmacokinetic profile of the mannitol doses proposed.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

Mannitol

The safety and tolerability of mannitol were reported in 433 patients receiving mannitol in comparative clinical trials. The most frequent adverse events (AE) reported in these trials were serum electrolyte changes, nausea and abdominal pain. Other AE's were vomiting, abdominal distension and increased haematocrit. In general safety and tolerability were comparable between mannitol and its comparators.

Intestinal gas levels were measured in 127 patients receiving mannitol in five clinical trials conducted between 1981 and 2016. In general, higher gas levels, especially of H_2, were measured in the mannitol patients if the procedure was performed without air insufflation, otherwise no differences were reported between mannitol and the comparators. No differences were found in O_2 and CH_4 levels.

A recent clinical study evaluated intestinal gas concentrations in three intestinal segments during introduction and withdrawal of the colonoscope with minimum air insufflation or suction. Intermittent infusions of small quantities of water were used as necessary. The study did not find elevated levels in any of the 50 patients examined with mannitol (*Paulo et al., 2016*).

To ensure patient safety in this study, colon H_2 and CH_4 concentrations will be measured during colonoscopy and all electrosurgical procedures will be avoided should gas concentrations reach potentially dangerous levels.

Anaphylactic/anaphylactoid reactions, as well as other hypersensitivity/infusion reactions have been reported with mannitol. Patients with known hypersensitivity to mannitol will be excluded from the study.

Patients with pre-existing renal disease, or those receiving potentially nephrotoxic drugs, are at increased risk of renal failure following administration of mannitol. Patients with severe renal disease will be excluded from this study.

Accumulation of mannitol (due to insufficient renal excretion) and dehydration due to diarrhoea may result in hypervolemia, overexpansion of extracellular fluid, which may lead to or exacerbate existing congestive heart failure. Patients with severe symptomatic congestive heart failure or recent ischemic heart disease will be excluded from this study.

Mannitol-induced osmotic diuresis and dehydration due to diarrhoea may cause or worsen dehydration/hypovolemia, haemoconcentration and electrolyte imbalances. Administration of mannitol may also cause hyperosmolality. Patients with pre-existing electrolyte disturbances will

be excluded from this study. Furthermore, electrolyte levels and plasma osmolality will be monitored throughout the study.

Laxatives are contraindicated in patients with bowel obstruction, therefore these patients and those with a history of colonic resection will be excluded from this study.

Of note, urine specific gravity may decrease because of osmotic diuresis caused by the well-known pharmacological profile of mannitol. Urine specific gravity out of normal ranges will be collected and managed as expected adverse event.

See the Investigator's Brochure for more details.

Polyethylene glycol + ascorbate (PEG ASC) (Moviprep®)

In the Moviprep® trials, abdominal distension, anal discomfort, thirst, nausea, vomiting, sleep disturbance and abdominal pain were the most common adverse reactions. Dehydration may occur as a result of diarrhoea and/or vomiting. Isolated cases of urticaria, rhinorrhoea, dermatitis, and anaphylactic reaction have been reported with PEG-based products.

Contraindications for the use of Moviprep®

- Hypersensitivity to the active ingredients or other components of Moviprep®
- Intestinal obstruction or perforation
- Gastric emptying disorders
- Ileus
- Phenylketonuria
- Glucose-6-phosphate dehydrogenase deficiency
- Toxic megacolon

Patients with contraindications will not be enrolled in this study.

Precautions for the use of polyethylene glycol + ascorbate (PEG ASC) (Moviprep®)

PEG-ASC should be administered with caution to fragile patients in poor health or patients with serious clinical impairment such as:

- Impaired gag reflex, or with a tendency to aspiration or regurgitation
- Impaired consciousness
- Severe renal insufficiency (creatinine clearance <30 mL/min)
- Cardiac impairment (NYHA grade III or IV)
- Patients at risk of arrhythmia, for example those on treatment for cardiovascular disease or who have thyroid disease
- Dehydration
- Severe acute inflammatory bowel disease

- The medicinal product contains aspartame, which is a source of phenylalanine. This may be harmful for people with phenylketonuria.

See the *simplified Investigational Medicinal Product Dossier (IMPD) for the reference product Moviprep®* for more details.

2.2.2 KNOWN POTENTIAL BENEFITS

The ideal method of bowel preparation for colonoscopy is a combination of effectiveness, safety, ease of self-administration, good patient acceptance and low cost. While current available preparations offer effectiveness and safety at a reasonable level, patient acceptance can still be improved. A bowel cleansing agent such as mannitol, which has a much better flavour than other cleansing agents, requires low volume and is self-administered the morning of the procedure (and thus does not interfere with sleep), is expected to improve patient compliance and thus the success of the procedure.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

In light of what outlined previously, the risk connected with this study is considered to be very low and is minimized by the use of a gas detector that will help performing electrocautery, if necessary, in safe conditions. Further information about the gas detector is available in the *Gas Detector Technical Documentation*. The expectation is to show that mannitol is not inferior to 2L PEG ASC in terms of bowel cleansing, while better in terms of patient acceptance. The development of oral mannitol for bowel cleansing and the conduct of this study are therefore justified.

3 OBJECTIVES AND ENDPOINTS

Phase II - Dose Finding/Pharmacokinetic sub-study	
Objectives	**Endpoints**
To determine the effective and safe dose of mannitol for adequate bowel cleansing to be used in the comparative non-inferiority phase of the study (phase III).	**Primary efficacy endpoint** • Proportion of patients with adequate bowel cleansing, defined as Boston Bowel Preparation Scale (BBPS) total score ≥6, with a score for each of the three colon segments (right; transverse, including flexures; and left, including sigmoid and rectum) ≥2 during colonoscopy after standard washing and air insufflation for luminal distension. **Secondary efficacy endpoint** • Caecal intubation rate, defined as the percentage of patients with appendiceal orifice visible to the endoscopist. **Safety and tolerability** • Proportion of patients in safe conditions, defined as the absence in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) of potentially dangerous levels of H_2 and/or CH_4 (>4% Vol and >100% of Lower Explosion Level (LEL), respectively) during colonoscopy after standard washing and air insufflation for luminal distension. • Incidence of adverse events from the beginning of study drug self-administration. • Proportion of patients with change from baseline considered clinically significant by the Investigator of haematological and chemical parameters (CBC, creatinine, BUN, eGFR, ALT, AST, glucose, electrolytes) 4 hours and 8 hours after completion of study drug self-administration, where clinically significant means that the change causes an additional control or a medical intervention. • Proportion of patients with change during colonoscopy considered clinically significant by the Investigator of vital signs (heart rate and pulse oximetry), where clinically significant means that the change causes an additional control or a medical intervention.

Phase II - Dose Finding/Pharmacokinetic sub-study	
Objectives	**Endpoints**
	Adherence and acceptability • Adherence: study drug completely taken, partially taken, not taken • Ease of use: numeric rating scale (NRS) (0 = very difficult to 10 = very easy) • Taste: NRS (0 = terrible to 10 = very good) • Willingness to reuse the preparation (yes/no)
To define the pharmacokinetic profile of the mannitol doses used in dose finding through a pharmacokinetic sub-study.	• C_{max}: maximum concentration • t_{max}: time to maximum concentration • AUC_0-t_{0-t}: area under concentration-time curve, from 0 to the last blood sampling time point with measurable concentration • $t_{1/2}$: elimination half-life

Phase III - Non-Inferiority	
Objectives	**Endpoints**
To demonstrate the non-inferiority of mannitol vs. standard split 2L PEG ASC (Moviprep®) in bowel cleansing for colonoscopy.	**Primary Efficacy endpoint** • Proportion of patients with adequate bowel cleansing, defined as BBPS total score ≥ 6, with a score for each of the three colon segments (right; transverse, including flexures; and left, including sigmoid and rectum) ≥ 2 during colonoscopy after standard washing and air insufflation for luminal distension. **Secondary efficacy endpoints** • Number, appearance, size, location and histological classification of neoplastic and inflammatory colorectal lesions detected. • Adenoma detection rate, defined as the percentage of patients with at least one lesion detected. • Caecal intubation rate, defined as the percentage of patients with appendiceal orifice visible to the endoscopist. • Ottawa Scale for bowel preparation before washing and air insufflation for luminal distension.
To assess the safety and tolerability of mannitol.	• Proportion of patients in safe conditions, defined as the absence in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that

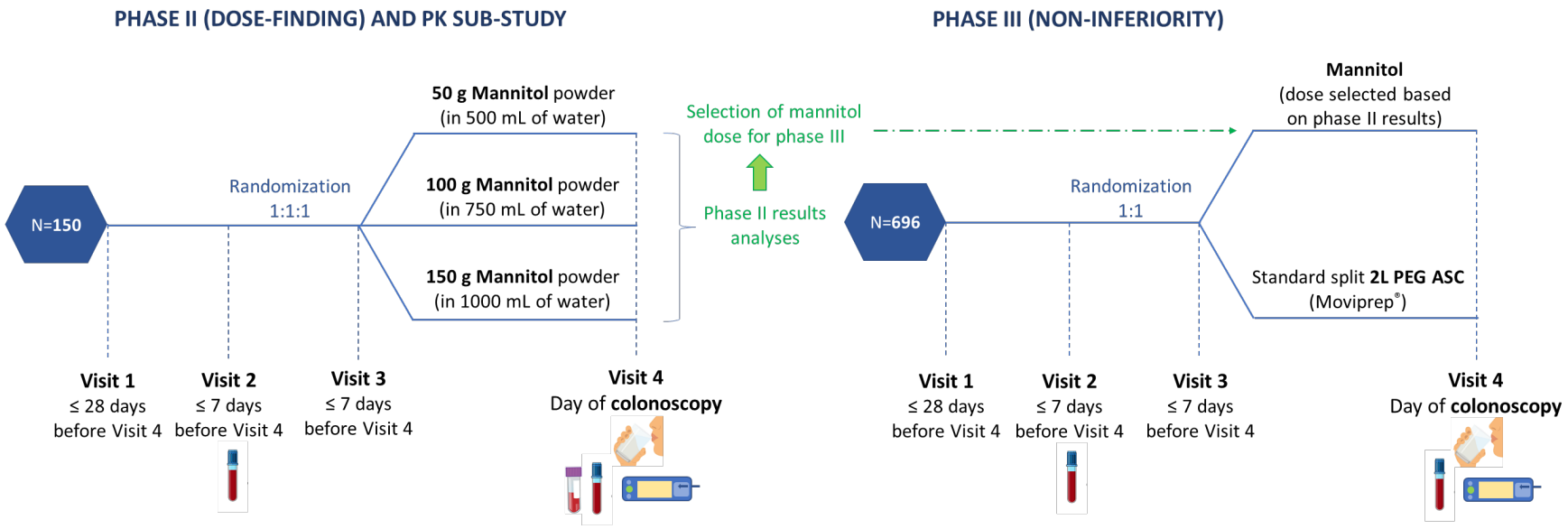
Phase III - Non-Inferiority	
Objectives	**Endpoints**
	prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) of potentially dangerous levels of H_2 and/or CH_4 (>4% Vol and >100% LEL, respectively) during colonoscopy after standard washing and air insufflation for luminal distension. • Incidence of adverse events from the beginning of study drug self-administration. • Proportion of patients with change from baseline considered clinically significant by the Investigator of haematological and chemical parameters (CBC, creatinine, BUN, eGFR, ALT, AST, glucose, electrolytes) 4 hours and 8 hours after completion of study drug self-administration, where clinically significant means that the change causes an additional control or a medical intervention. • Proportion of patients with change from baseline considered clinically significant by the Investigator of vital signs (heart rate, systolic and diastolic blood pressure) measured during visits, as well as clinically significant change of pulse oximetry and heart rate measured during colonoscopy and systolic and diastolic blood pressure measured immediately prior and after colonoscopy, where clinically significant means that the change causes an additional control or a medical intervention. Of note, clinically significant changes of systolic and diastolic blood pressure measured during colonoscopy will also be reported if considered clinically significant by the Investigator.
To evaluate adherence to and acceptability of bowel preparation with mannitol and with Moviprep®.	• Adherence: study drug completely taken, partially taken, not taken • Bowel Cleansing Impact Review (BOCLIR) (only at Italian centres) • Ease of use: NRS (0 = very difficult to 10 = very easy) • Taste: NRS (0 = terrible to 10 = very good) • Willingness to reuse the preparation (yes/no)

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a phase II/III, international, multicentre, randomized, parallel-group, endoscopist-blinded study that combines a phase II dose-finding study/pharmacokinetic sub-study with a phase III non-inferiority efficacy study (see *Figure 4-1*). The population for phase III will not include the patients who participated in phase II.

Figure 4-1 Study design



Study drug self-administration:
Mannitol: in the morning on the day of colonoscopy, to be completed at least 4h before colonoscopy.
2L PEG ASC: in the evening before colonoscopy (1L) and in the morning on the day of colonoscopy (1L), to be completed at least 4h before colonoscopy

Blood sampling for standard haematology, clinical chemistry and electrolyte levels (on Visit 4: 4h and 8h after end of study drug self-administration)

ONLY FOR PK SUB-STUDY PATIENTS (at least 10/group) additional blood sampling for PK: before, 1h, 2h, 4h and 8h after end of mannitol self-administration on Visit 4

Measurements of intestinal gas concentrations (H_2, CH_4 and O_2) using a multi-gas detector (Dräger X-am® 8000)

In both phases, the study drugs will not be blinded, but all endoscopists performing study colonoscopies will not be aware of group allocation; patients and site personnel involved in the randomization of the patient and management of the study drugs will be instructed not to disclose group allocation to the endoscopists. Experienced endoscopists will undergo specific training to decrease inter-observer variability in the evaluation of bowel cleansing and to refine intestinal gas measurement techniques.

Details of all the assessments to be performed are available in the schedule of activities (SoA) in *Section 1.2* and in *Section 8*.

4.1.1 PHASE II

The parallel-group dose-finding phase will be conducted at approximately 8 centres and will involve 150 patients randomly assigned (1:1:1 ratio) to one of the following three treatment groups:

- 50 g mannitol powder to be dissolved in 500 ml of water
- 100 g mannitol powder to be dissolved in 750 ml of water
- 150 g mannitol powder to be dissolved in 1000 ml of water

Of note, these doses of mannitol have been selected as this range includes the minimum (50 g) and maximum (150 g) mannitol doses used effectively in the proposed indication, as reported in published literature. Please refer to *Section 2.1* for further details.

Randomization is stratified by centre and by the presence of constipation (yes/no), defined as the recurrent use of laxatives or Bristol Stool Form Scale (BSFS) < 3 in the two weeks prior to randomisation.

To limit patient exposure to an ineffective dose causing repetition of colonoscopy, the adequacy of bowel cleansing will be monitored continuously and enrolment in a treatment group will be discontinued as soon as 25% of treated patients present inadequate bowel cleansing causing repetition of colonoscopy. The stopping rule, mainly guided by clinical considerations, will be applied in each treatment group as follows:

- Up to the 25th enrolled patient, enrolment in a treatment group will be stopped as soon as 6 patients present inadequate bowel cleansing causing repetition of colonoscopy (i.e. if among the initial 15 patients enrolled in a treatment group, 6 need to repeat the cleansing procedure, the treatment group will be immediately discontinued).
- From the 26th enrolled patient on (if treatment was not discontinued earlier), enrolment will be stopped as soon as 25% of patients present inadequate bowel cleansing causing repetition of colonoscopy (i.e. if among the initial 32 patients enrolled in a treatment group, 8 need to repeat the cleansing procedure, the treatment group will be immediately discontinued).

The appropriate mannitol dose to be used in the comparative non-inferiority phase (phase III) will be singled out at the end of dose-finding based on the following criteria:

- 75% or greater rate of adequate bowel cleansing.
- Rate of patients in safe conditions, defined as absence of potentially dangerous levels of H_2 and CH_4 in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension).
- Clinical judgment based on the caecal intubation rate, the incidence of adverse events, treatment adherence and acceptability (considering ease of use, taste and willingness to reuse the preparation).

Should two or all three doses prove to be equally safe and effective, the lowest dose will be selected for phase III of the study.

Study visits

Phase II of the study consist of four visits:

Visit 1 (≤ 28 days before the day of colonoscopy): after signed written informed consent is obtained, information concerning demographics, medical history, concomitant medications and indications for colonoscopy will be collected in the electronic case report form (eCRF). The incidence of adverse events will be recorded.

Visit 2 (≤ 7 days before the day of colonoscopy): to complete the verification of inclusion/exclusion criteria, a blood sample will be drawn to assess the haematological and chemical parameters (including electrolyte levels) of all patients and to perform a pregnancy test for women of childbearing potential. Assessments include a urinalysis and the measurement of vital signs (blood pressure and heart rate). The incidence of adverse events will be recorded.

Visit 3 (≤ 7 days before the day of colonoscopy): if inclusion/exclusion criteria are met, the Bristol Stool Form Scale (BSFS) will be administered, randomization will be performed, study drug will be dispensed and verbal and written instructions for its use will be provided. The date and time of colonoscopy will be communicated and reported on a form given to the patient. On the same form, patients will indicate date and time of start and end of study drug self-administration. The incidence of adverse events will be recorded.

More than one visit may take place on the same day.

Visit 4 (day of colonoscopy):

A blood and urine sample will be collected at the following time points:

- 4 hours ± 30 minutes after the end of study drug self-administration
- 8 hours ± 30 minutes after the end of study drug self-administration

After completion of bowel preparation, prior to colonoscopy, patients will fill in the questionnaire on acceptability and adherence.

The blinded endoscopist will then perform the scheduled colonoscopy using a standard colonoscope recording data on bowel cleansing using the BBPS and measuring intestinal gas concentrations in each colon segment after standard washing and air insufflation. Of note, CO_2 insufflation and water-aided techniques for colon distension (e.g. water immersion, water exchange) will not be allowed. The endoscopist will also confirm caecal intubation, defined as identification of the appendiceal orifice. Drugs administered for the procedure will be recorded.

Intestinal gas (H_2, CH_4 and O_2) concentrations in each segment will be measured using a multi-gas detector (Dräger X-am® 8000). Further information is available in the *Gas Detector Technical Documentation*. Use of any electrocautery device is allowed only during withdrawal and after washing and air insufflation. If H_2 and/or CH_4 levels are potentially dangerous, any electrosurgical procedure must be avoided.

Vital signs (heart rate and blood pressure) will be measured prior to colonoscopy. Oxygen saturation and heart rate will be measured continuously during colonoscopy, but only clinically significant abnormal findings will be recorded on the eCRF, where clinically significant means that these abnormal findings cause an additional control or a medical intervention.

The incidence of adverse events will be recorded.

4.1.2 PHASE II - PHARMACOKINETIC SUB-STUDY

Patients accepting to be included in the sub-study of phase II will be enrolled sequentially until the required sample size (10 evaluable patients in each dose group) is reached. If patients do not undergo all PK evaluations, the sub-study sample size will be increased to guarantee at least 8 PK evaluations for each assessment time.

Dietary restrictions based on the INRAN tables (*Carnovale and Marletta 2007*) are required, after overnight fasting, between 24 hours before and the start of mannitol self-administration. Thus, foods containing a significant amount of soluble sugars are to be forbidden for the PK sub-study. Patients enrolled in the pharmacokinetic sub-study have to avoid any food intake and drink only water between the start of mannitol self-administration and 8 hours after mannitol intake. Of note, between 4 and 8 hours after mannitol intake, patients may eat any food devoid of soluble sugars according to the INRAN tables, if deemed necessary by the Investigator. Patients will be allowed to eat without restrictions 8 hours after drug self-administration.

Study visits

Patients enrolled in the pharmacokinetic sub-study will follow the same scheme of phase II of the study that consists of four visits:

Visit 1 (≤ 28 days before the day of colonoscopy): after signed written informed consent is obtained, information concerning demographics, medical history, concomitant medications and indications for colonoscopy will be collected in the electronic case report form (eCRF). The incidence of adverse events will be recorded.

Visit 2 (≤ 7 days before the day of colonoscopy): to complete the verification of inclusion/exclusion criteria, a blood sample will be drawn to assess the haematological and chemical parameters (including electrolyte levels) of all patients and to perform a pregnancy test for women of childbearing potential. Assessments include a urinalysis and the measurement of vital signs (blood pressure and heart rate). The incidence of adverse events will be recorded.

Visit 3 (≤ 7 days before the day of colonoscopy): if inclusion/exclusion criteria are met, the Bristol Stool Form Scale (BSFS) will be administered, randomization will be performed, study drug will be dispensed and verbal and written instructions for its use will be provided. The date and time of colonoscopy will be communicated and reported on a form given to the patient. On the same form, patients will indicate date and time of start and end of study drug self-administration. The incidence of adverse events will be recorded.

More than one visit may take place on the same day.

Visit 4 (day of colonoscopy):

A blood and urine sample will be collected at the following time points:

- 4 hours ± 30 minutes after the end of study drug self-administration
- 8 hours ± 30 minutes after the end of study drug self-administration

In addition, in order to measure mannitol blood levels, venous blood samples will be drawn at the following times:

- T_0 (baseline, before mannitol self-administration)
- T_1 (1 hour ± 5 min after completion of mannitol self-administration)
- T_2 (2 hours ± 5 min after completion of mannitol self-administration)
- T_4 (4 hours ± 10 min after completion of mannitol self-administration, before colonoscopy)
- T_8 (8 hours ± 10 min after completion of mannitol self-administration, after colonoscopy)

After completion of bowel preparation, prior to colonoscopy, patients will fill in the questionnaire on acceptability and adherence.

The blinded endoscopist will then perform the scheduled colonoscopy using a standard colonoscope recording data on bowel cleansing using the BBPS and measuring intestinal gas concentrations in each colon segment after standard washing and air insufflation. Of note, CO_2 insufflation and water-aided techniques for colon distension (e.g. water immersion and water exchange) will not be allowed. The endoscopist will also confirm caecal intubation, defined as identification of the appendiceal orifice. Drugs administered for the procedure will be recorded.

Intestinal gas concentrations in each segment will be measured using a multi-gas detector (Dräger X-am® 8000). Please refer to the *Gas Detector Technical Documentation* for further details. Use of any electrocautery device is allowed only during withdrawal and after washing and air insufflation. If H_2 and/or CH_4 levels are potentially dangerous, any electrosurgical procedure must be avoided.

Vital signs (heart rate and blood pressure) will be measured prior to colonoscopy. Oxygen saturation and heart rate will be measured continuously during colonoscopy, but only clinically significant abnormal findings will be recorded on the eCRF, where clinically significant means that these abnormal findings cause an additional control or a medical intervention.

The incidence of adverse events will be recorded.

4.1.3 PHASE III

A parallel-group design will be implemented to test the non-inferiority of bowel cleansing with the mannitol dose selected in phase II against standard split 2-liter polyethylene glycol plus ascorbate solution (Moviprep®). Phase III will begin only once all data collected from phase II necessary for establishing the optimal mannitol dose have been analysed. The non-inferiority study will be conducted in 4 countries (Italy, Germany, Russia and France) and involve 696 subjects randomized in a 1:1 ratio to one of the two study drugs. Randomization will be stratified by centre.

Study visits

Phase III of the study consists of four visits:

Visit 1 (≤ 28 days before the day of colonoscopy): after signed written informed consent is obtained, information concerning demographics, medical history, concomitant medications and indications for colonoscopy will be collected in the electronic case report form (eCRF). The incidence of adverse events will be recorded.

Visit 2 (≤ 7 days before the day of colonoscopy): to complete the verification of inclusion/exclusion criteria, a blood sample will be drawn to assess the haematological and chemical parameters (including electrolyte levels) of all patients and to perform a pregnancy test for women of childbearing potential. Assessments include a urinalysis and the measurement of vital signs (blood pressure and heart rate). The incidence of adverse events will be recorded.

Visit 3 (≤ 7 days before the day of colonoscopy): if inclusion/exclusion criteria are met, randomization will be performed, study drug will be dispensed and verbal and written instructions for its use will be provided. The date and time of colonoscopy will be communicated and reported on a form given to the patient. On the same form, patients will indicate date and time of start and end of study drug self-administration. The incidence of adverse events will be recorded.

More than one visit may take place on the same day.

Visit 4 (day of colonoscopy):

A blood and urine sample will be collected at the following time points:

- 4 hours ± 30 minutes after the end of study drug self-administration
- 8 hours ± 30 minutes after the end of study drug self-administration

After completion of bowel preparation, prior to colonoscopy, patients will fill in the questionnaire on acceptability and adherence. The Bowel Cleansing Impact Review (BOCLIR) is also to be completed, but only by patients enrolled at Italian centres.

The blinded endoscopist will then perform the scheduled colonoscopy using a standard colonoscope recording data on bowel cleansing using the BBPS and Ottawa scale. The endoscopist will confirm caecal intubation, defined as identification of the appendiceal orifice, and record the number, appearance, size, location and histological type of neoplastic and inflammatory colorectal lesions detected.

The endoscopist will measure intestinal gas concentrations in each colon segment after standard washing and air insufflation. Of note, CO_2 insufflation and water-aided techniques for colon distension (e.g. water immersion and water exchange) will not be allowed. H_2, CH_4 and O_2 levels are also to be measured following the introduction of the colonoscope in the sigmoidal-rectum junction (15-25 cm from anal margin) before standard washing and air insufflation. Drugs administered for the procedure will be recorded.

Intestinal gas concentrations in each segment will be measured using a multi-gas detector (Dräger X-am® 8000). Detailed information is available in the *Gas Detector Technical Documentation.* Use of any electrocautery device is allowed only during withdrawal and after washing and air insufflation. If H_2 and/or CH_4 levels are potentially dangerous, any electrosurgical procedure must be avoided.

Vital signs (heart rate and blood pressure) will be measured prior to colonoscopy. Oxygen saturation, blood pressure and heart rate will be measured during colonoscopy, but only clinically significant abnormal findings of oxygen saturation and heart rate measured during colonoscopy and blood pressure measured immediately prior and after colonoscopy will be recorded on the eCRF, where clinically significant means that these abnormal findings cause an additional control

or a medical intervention. Of note, clinically significant changes of blood pressure measured during colonoscopy will also be reported if considered clinically significant by the Investigator.

The incidence of adverse events will be recorded.

4.2 END OF STUDY DEFINITION

A participant is considered as having completed the study if he or she has completed the procedures in the SoA. Of note, the results of the laboratory tests performed at Visit 4 (day of colonoscopy) and the histological evaluation of colorectal lesions detected during colonoscopy will be available after the participant has completed the last procedure of the study on the day of colonoscopy. The end of the phase II/III study is defined as completion of the last procedure in the trial globally, namely the last visit of the last patient enrolled in the phase III study (i.e. last patient last visit, LPLV).

5 STUDY POPULATION

The study population is made up of 846 adult patients scheduled for elective (screening, surveillance or diagnostic) colonoscopy; 50 patients in each of the three mannitol dose groups for phase II, and 348 patients in each of the two treatment groups for phase III (the selected mannitol dose and 2L PEG ASC). The population for phase III will not include the patients who participated in phase II.

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, a subject must meet all the following criteria:

1. Ability of patient to consent and provide signed written informed consent
2. Age ≥18 years
3. Males and females scheduled for elective (screening, surveillance or diagnostic) colonoscopy to be prepared and performed according to ESGE guidelines
4. Patients willing and able to complete the entire study and to comply with instructions

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Pregnancy or breast feeding. Females of childbearing potential must have a negative pregnancy test at Visit 2 and must practice one of the following methods of birth control throughout the study period (unless postmenopausal or surgically sterile, or whose sole sexual partner has had a successful vasectomy): oral, implantable, or injectable contraceptives (for a minimum of three months before study entry) in combination with a condom; intrauterine device in combination with a condom; double barrier method (condom and occlusive cap with spermicidal foam/gel/film/cream/suppository).
2. Severe renal failure: glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2 estimated by means of simplified MDRD equation.
3. Severe heart failure: NYHA Class III-IV.
4. Severe anaemia (Hb ≤8 g/dl).
5. Severe acute and chronically active Inflammatory Bowel Disease; patients in clinical remission (Crohn's Disease Activity Index - CDAI < 150 for Crohn Disease (*Best et al., 1976*) and Partial Mayo Score ≤ 2 for Ulcerative Colitis (*Schroeder et al., 1987*)) are allowed.
6. Chronic liver disease Child-Pugh class B or C.
7. Electrolyte disturbances (Na, Cl, K, Ca or P out of normal ranges)
8. Recent (<6 months) symptomatic acute ischemic heart disease.

9. History of significant gastrointestinal surgeries, including colon resection, sub-total colectomy, abdominoperineal resection, de-functioning colostomy or ileostomy, Hartmann's procedure and other surgeries involving the structure and function of the colon.
10. Use of laxatives, colon motility altering drugs and/or other substances (e.g. simethicone) that can affect bowel cleansing or visibility during colonoscopy within 24 hours prior to colonoscopy.
11. Suspected bowel obstruction or perforation.
12. Indication for partial colonoscopy.
13. Patients who have received an investigational drug or therapy within 5 half-lives of the first visit.
14. Patients previously screened for participation in this study.
15. Hypersensitivity to the active ingredients or to any of the excipients of the study drugs.
16. Contraindications to Moviprep® (only for phase III).

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but do not subsequently begin the investigational treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

- Test (phase II and phase III): mannitol solution (Pearlitol® PF)
- Standard: (phase III): polyethylene glycol plus ascorbate solution (2L PEG ASC) (Moviprep®)

6.1.2 DOSING AND ADMINISTRATION

Patients should be advised to allow for appropriate time to travel to the colonoscopy unit.

Upon enrolment, patients will be instructed on what food and drinks are allowed and forbidden for bowel preparation according to the procedures applied at each centre. The use of prokinetic agents as adjuncts to bowel preparation is not recommended.

Dietary recommendations as per local practice at the centre should be followed prior to colonoscopy. In addition, it is strongly recommended that additional liquids should be drunk following treatment according to local practice at the centre.

Patients enrolled in the pharmacokinetic sub-study should drink only one litre of water. Moreover, as mannitol is contained in foods in a certain amount, to minimize the error of measuring mannitol plasma concentration after the intake of the investigational drug, dietary restrictions based on the INRAN tables (*Carnovale and Marletta 2007*) are required, after overnight fasting, between 24 hours before and the start of mannitol self-administration. Thus, foods containing a significant amount of soluble sugars are to be forbidden for the PK sub-study. Patients enrolled in the pharmacokinetic sub-study have to avoid any food intake and drink only water between the start of mannitol intake and 8 hours after drug self-administration. Of note, between 4 and 8 hours after mannitol intake, patients may eat any food devoid of soluble sugars according to the INRAN tables, if deemed necessary by the Investigator. Patients will be allowed to eat without restrictions 8 hours after mannitol self-administration.

Mannitol

Patients will be randomly assigned to one of the following three treatment groups in a 1:1:1 ratio:

- 50 g mannitol powder
- 100g mannitol powder
- 150g mannitol powder

The product must be dissolved in water prior to self-administration as follows:

1) Open the sachet and pour the mannitol powder in a container larger than one litre.

2) Add room temperature water in the recommended amount for each dosage according to the table below and stir until the powder is completely dissolved (about 5 minutes).

Mannitol per Dose (g)	**Water for dose reconstitution (mL)**	**Concentration (g/mL) after reconstitution**
50	500	0.10
100	750	0.13
150	1000	0.15

3) Drink the prepared solution within 30 minutes for 50 and 100 g doses and 60 minutes for the 150 g dose.

4) Drink about one litre of clear liquid in the next hour according to local practice at the centre to prevent dehydration. Patients enrolled in the pharmacokinetic sub-study should drink only one litre of water in the next hour and follow the dietary restrictions and fasting instructions previously described.

Participants will be instructed to drink mannitol **the day of the colonoscopy** and self-administration must be completed at least 4 hours before colonoscopy.

2L PEG ASC (Moviprep®)

The route of administration is oral. One treatment consists of two litres of Moviprep® taken according to split-dose regimen. During treatment it is strongly recommended to drink about half a litre (500 mL) of clear liquid after each litre of Moviprep® to prevent dehydration, according to local practice at the centre.

The first litre of Moviprep® is prepared by dissolving one sachet A and one sachet B together in water to make one litre of solution. The reconstituted solution must be drunk over a period of one to two hours the **evening before colonoscopy**. About half a litre of clear liquid should be drunk in the next hour to prevent dehydration according to local practice at the centre. This process should be repeated with a second litre of Moviprep® prepared by dissolving one sachet A and one sachet B together in water to make one litre of solution in the early morning of the **day of the procedure**. As previously mentioned, about half a litre of clear liquid should be drunk in the next hour to prevent dehydration according to local practice at the centre. Ensure consumption of Moviprep® as well as of any other clear fluids has finished at least four hours before the start of colonoscopy.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Study drugs will be provided by the Sponsor. An unblinded Investigator, or a pharmacist or other appropriate individual who is designated by the Investigator, will maintain accurate records of study drug delivery to the study site, the inventory at the site, the use for each subject, and the return to the sponsor or alternative disposition of unused products.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Mannitol: powder for oral solution packaged in sachets.

The quali-quantitative composition of Pearlitol® PF is 100% mannitol powder.

Moviprep®: powder for oral solution packaged in two sachets:

Sachet A contains the following active ingredients:

- Macrogol 3350: 100 g
- Sodium sulfate: 7.5 g
- Sodium chloride: 2.691 g
- Potassium chloride: 1.015 g

Sachet B contains the following active ingredients:

- Ascorbic acid: 4.7 g
- Sodium ascorbate: 5.9 g

Excipients with known effect:

- Aspartame: 0.175 g
- Dextrose: 0.120 g

Study drug labels will comply with legal requirements and will be printed in the local language.

6.2.3 DRUG STORAGE AND STABILITY

Sachets of mannitol are to be stored at a temperature below 25°C. Reconstituted solutions are also to be stored below 25°C. Solutions should be kept covered.

Sachets of PEG-ASC are to be stored at a temperature below 25°C. Reconstituted solutions are also to be stored below 25°C and may be refrigerated. Solutions should be kept covered.

6.2.4 PREPARATION

Mannitol and PEG ASC are to be prepared by stirring the powder in amounts of room temperature water as indicated in *Section 6.1.2*.

6.3 STUDY INTERVENTION COMPLIANCE

Subjects will be asked to return all unused drug at the visit prior to colonoscopy. Adherence to protocol instructions will be evaluated prior to colonoscopy.

6.4 CONCOMITANT MEDICATIONS

Medications to be reported on the eCRF are concomitant prescription medications, over-the-counter medications and supplements.

6.4.1 PROHIBITED CONCOMITANT MEDICATIONS

The use of laxatives, colon motility altering drugs and/or other substances (e.g. simethicone) that can affect bowel cleansing or visibility during colonoscopy within 24 hours prior to colonoscopy is prohibited.

6.4.2 PERMITTED CONCOMITANT MEDICATIONS

All concomitant medications related to either pre-existing medical conditions (which are already present at baseline or occur after baseline prior to the day of colonoscopy) or execution of colonoscopy (such as analgesic and sedative drugs) are permitted and are to be reported separately on the eCRF.

6.4.3 RESCUE THERAPY

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a clinically significant finding is identified after enrolment, the Investigator or qualified designee will determine if any change in participant management is needed. Any new clinically significant finding leading to discontinuation from study treatment will be reported as an adverse event (AE).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy.
- If any AE or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF.

7.3 LOST TO FOLLOW-UP

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw from the study, the Investigator should make every effort to contact the patient, family or family physician and document the steps taken to contact the patient, e.g. dates of telephone calls, etc. Patients lost to follow up should be recorded as such on the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ASSESSMENTS

A schedule of assessments is available in *Section 1.2*

8.1.1 PHASE II

The following assessments will be performed during phase II of the study:

- Informed consent, demographic features (age, sex and ethnicity), medical history and indication for colonoscopy are collected at Visit 1.
- Fulfilment of inclusion/exclusion criteria is definitively assessed at Visit 3.
- Evaluation of bowel preparation – Boston Bowel Preparation Scale (BBPS)

The BBPS was developed to limit inter-observer variability in the rating of bowel preparation quality, while preserving the ability to distinguish various degrees of bowel cleanliness. Subjective terms such as “excellent,” “good,” “fair,” “poor,” and “unsatisfactory” are replaced by a four-point scoring system applied to each of the three broad regions of the colon: the right colon (including the cecum and ascending colon), the transverse colon (including the hepatic and splenic flexures), and the left colon (including the descending colon, sigmoid colon, and rectum). The points are assigned as follows:

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

Each of the three segments of the colon (right, transverse, left) is thus scored from 0 to 3, with total score ranging from 0 to 9, and is to be completed at Visit 4 after standard washing and air insufflation for luminal distension.

See *Appendix 1* for a visual representation of BBPS scoring.

- Confirmation of caecal intubation, defined as identification of the appendiceal orifice.
- Measurement of intestinal gas concentrations

Intestinal H_2, CH_4 and O_2 concentrations will be measured in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectal junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension using a multi-gas detector (Dräger X-am® 8000). The gas detector has no direct contact with the patient's body but is connected through a one-way pump and a filter to a polyvinyl catheter inserted into the working channel of the colonoscope. The intestinal gases are conveyed to the gas detector by a one-way pump that prevents the return of gases to the colonoscope. Further information is available in the *Gas Detector Technical Documentation.* Use of any electrocautery device is allowed only during withdrawal and after washing and air insufflation. If H_2 and/or CH_4 levels are potentially dangerous, any electrosurgical procedure must be avoided.

- Vital signs (heart rate, systolic and diastolic pressure) are measured at Visit 2 and at Visit 4 prior to colonoscopy.
- Clinically significant abnormal oxygen saturation and heart rate values obtained during colonoscopy will be recorded on the eCRF, where clinically significant means that these abnormal findings cause an additional control or a medical intervention.
- Standard haematology, clinical chemistry and urinalysis tests are performed at Visit 2 and Visit 4. See *Section 8.1.4* for details. A blood beta hCG pregnancy test is required for women of childbearing potential at Visit 2.
- Bristol Stool Form Scale

The Bristol Stool Form Scale (BSFS) is a 7-point scale (from 1 = separate hard lumps, like nuts [hard to pass] to 7 = watery, no solid pieces [entirely liquid]) used extensively in clinical practice and research for stool form measurement and has undergone validity and reliability testing (*Blake et al, 2016*). The BSFS is evaluated at Visit 3. See *Appendix 2*.

- Patient reported outcomes

The following information will be collected from the patient through patient questionnaires at Visit 4 following completion of study drug self-administration but prior to colonoscopy:

  - Adherence: study drug completely taken, partially taken, not taken
  - Ease of use: NRS (0 = very difficult to 10 = very easy)
  - Taste: NRS (0 = terrible to 10 = very good)
  - Intention to reuse the preparation (yes/no)

- Concomitant medications are collected at each visit, drugs for colonoscopy at Visit 4.
- The incidence of adverse events will be recorded.

8.1.2 PHASE II - PHARMACOKINETIC SUBSTUDY

The following assessments will be performed in patients participating in the phase II pharmacokinetic sub-study:

- Informed consent, demographic features (age, sex and ethnicity), medical history and indication for colonoscopy are collected at Visit 1.
- Fulfilment of inclusion/exclusion criteria is definitively assessed at Visit 3.
- Evaluation of bowel preparation – Boston Bowel Preparation Scale (BBPS)

The BBPS was developed to limit inter-observer variability in the rating of bowel preparation quality, while preserving the ability to distinguish various degrees of bowel cleanliness. Subjective terms such as "excellent," "good," "fair," "poor," and "unsatisfactory" are replaced by a four-point scoring system applied to each of the three broad regions of the colon: the right colon (including the cecum and ascending colon), the transverse colon (including the hepatic and splenic flexures), and the left colon (including the descending colon, sigmoid colon, and rectum). The points are assigned as follows:

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

Each of the three segments of the colon (right, transverse, left) is thus scored from 0 to 3, with total score ranging from 0 to 9, and is to be completed at Visit 4 after standard washing and air insufflation for luminal distension.

See *Appendix 1* for a visual representation of BBPS scoring.

- Confirmation of caecal intubation, defined as identification of the appendiceal orifice.
- Measurement of intestinal gas concentrations

Intestinal H_2, CH_4 and O_2 concentrations will be measured in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectal junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension

using a multi-gas detector (Dräger X-am® 8000) not directly connected to the patient. See *Section 8.1.1* and the *Gas Detector Technical Documentation* for further details.

- Vital signs (heart rate, systolic and diastolic pressure) are measured at Visit 2 and at Visit 4 prior to colonoscopy.
- Clinically significant abnormal oxygen saturation and heart rate values obtained during colonoscopy will be recorded on the eCRF, where clinically significant means that these abnormal findings cause an additional control or a medical intervention.
- Standard haematology, clinical chemistry and urinalysis tests are performed at Visit 2 and Visit 4. See *Section 8.1.4* for details. A blood beta hCG pregnancy test is required for women of childbearing potential at Visit 2.
- Blood sampling for pharmacokinetics

In order to measure blood levels of mannitol, patients participating in the pharmacokinetic sub-study will have blood draws before mannitol self-administration (T_0 - baseline), and 1 hour (T_1), 2 hours (T_2), 4 hours (T_4) and 8 hours (T_8) after completion of mannitol self-administration.

The tubes containing the blood samples are to be gently inverted a few times for complete mixing with the anticoagulant and maintained in refrigerated conditions until shipment to the centralized bioanalytical laboratory (see Study Manual for details).

- Bristol Stool Form Scale

The Bristol Stool Form Scale (BSFS) is a 7-point scale (from 1 = separate hard lumps, like nuts [hard to pass] to 7 = watery, no solid pieces [entirely liquid]) used extensively in clinical practice and research for stool form measurement and has undergone validity and reliability testing (*Blake et al, 2016*). The BSFS is evaluated at Visit 3. See *Appendix 2*.

- Patient reported outcomes

The following information will be collected from the patient through patient questionnaires at Visit 4 following completion of study drug self-administration but prior to colonoscopy:

  - Adherence: study drug completely taken, partially taken, not taken
  - Ease of use: NRS (0 = very difficult to 10 = very easy)
  - Taste: NRS (0 = terrible to 10 = very good)
  - Intention to reuse the preparation (yes/no)

- Concomitant medications are collected at each visit, drugs for colonoscopy at Visit 4.
- The incidence of adverse events will be recorded.

8.1.3 PHASE III

The following assessments will be performed during phase III of the study:

- Informed consent, demographic features (age, sex and ethnicity), medical history and indication for colonoscopy are collected at Visit 1.
- Fulfilment of inclusion/exclusion criteria is definitively assessed at Visit 3.
- Evaluation of bowel preparation – Boston Bowel Preparation Scale (BBPS)

The BBPS is to be completed at Visit 4 after standard washing and air insufflation for luminal distension. See *Section 8.1.1* for scoring details and *Appendix 2* for a visual representation of BBPS scoring

- Evaluation of bowel preparation – Ottawa Scale (OS)

The OS total score ranges from 0 to 14 and is calculated by adding up the scores for each of the three segments of the colon (right, middle, left including sigmoid and rectum), each receiving a score on a 5-point scale (0-4), where 0 = perfect preparation, 1 = presence of clear liquid that does not require suction, 2 = presence of liquid that must be suctioned, 3 = presence of stool that must be flushed, 4 = presence of not-washable stool plus the overall amount of colonic fluid graded using a 3-point scale (0-2). Adequate preparation = OS < 6 (*Rostom et al., 2004*). The evaluation is performed at Visit 4 before washing and air insufflation for luminal distension. See *Appendix 3* for a visual representation of Ottawa Scale scoring.

- Colorectal lesions

The following features of colorectal lesions detected during colonoscopy at Visit 4 are to be recorded on the eCRF:

  - Number
  - Appearance (peduncolated, not peduncolated)
  - Size (<5 mm, 5-9 mm, 10-19 mm, ≥20 mm)
  - Location (right; transverse, including flexures; and left, including sigmoid and rectum)
  - Histological classification (hyperplastic; inflammatory; tubular adenoma with low grade (LG) dysplasia <10 mm or ≥10 mm; tubular adenoma with high grade (HG) dysplasia <10 mm or ≥10 mm; adenoma with villous component >20% with LG or HG dysplasia; sessile serrated adenoma; adenoma; advanced adenoma; invasive cancer)

- Confirmation of caecal intubation, defined as identification of the appendiceal orifice.
- Measurement of intestinal gas concentrations

Intestinal H_2, CH_4 and O_2 concentrations will be measured in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at sigmoidal-rectal junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension using a multi-gas detector (Dräger X-am® 8000) not directly connected to the patient. See *Section 8.1.1* and the *Gas Detector Technical Documentation* for further details.

Intestinal H_2, CH_4 and O_2 concentrations will be measured following the introduction of the colonoscope in the sigmoidal-rectum junction (15-25 cm from anal margin) also before standard washing and air insufflation.

- Vital signs (heart rate, systolic and diastolic pressure) are measured at Visit 2 and at Visit 4 prior to colonoscopy.
- Clinically significant abnormal oxygen saturation and heart rate values obtained during colonoscopy, as well as clinically significant abnormal systolic and diastolic blood pressure values obtained immediately prior and after colonoscopy will be recorded on the eCRF, where clinically significant means that these abnormal findings cause an additional control or a medical intervention. Of note, clinically significant changes of systolic and diastolic blood pressure measured during colonoscopy will also be reported if considered clinically significant by the Investigator.
- Standard haematology, clinical chemistry and urinalysis tests are performed at Visit 2 and Visit 4. See *Section 8.1.4* for details. A blood beta hCG pregnancy test is required for women of childbearing potential at Visit 2.
- Bowel Cleansing Impact Review (BOCLIR) (Italian sites only).

The BOCLIR is a measure of the acceptability and tolerability of bowel cleansers consisting of three unidimensional scales (satisfaction, symptoms and activity limitations) with good psychometric and scaling properties. Item responses are summed to provide scale scores. In the final validated Italian version of BOCLIR, the satisfaction scale contains eight items (each item using a 4-point scale from 0 to 3) and the score ranges from 0 (highly satisfied) to 24 (highly dissatisfied). The symptoms scale includes 14 items (each item using a 4-point scale from 0 to 3) and the score ranges from 0 (no symptoms) to 42 (severe symptoms). The activity limitations scale is made up of 12 items (each item using a 4-point scale from 0 to 3) and the score ranges from 0 (no effect on activities) to 36 (activities greatly affected). The total score is the sum of the three scales and ranges from 0 to 102. Patients who report a worse experience in terms of the three factors score higher on the BOCLIR scale. The BOCLIR allows accurate assessment of patient response to bowel cleansing preparations (*Doward et al., 2013*). The BOCLIR questionnaire is completed at Visit 4 by patients following completion of study drug self-administration but prior to colonoscopy at Italian sites because only the Italian language version is validated for use in clinical trials.

- Patient reported outcomes

The following information will be collected from the patient through questionnaires at Visit 4 following completion of the bowel cleansing procedure but prior to colonoscopy:

  - Adherence: study drug completely taken, partially taken, not taken
  - Ease of use: NRS (0 = very difficult to 10 = very easy)
  - Taste: NRS (0 = terrible to 10 = very good)
  - Intention to reuse the preparation (yes/no)

- Concomitant medications are collected at each visit, drugs for colonoscopy at Visit 4.
- The incidence of adverse events will be recorded.

8.1.4 LABORATORY TESTS (PHASE II AND PHASE III)

Standard urinalysis, haematological and blood chemistry tests will be performed at Visit 2 (pre-colonoscopy visit) and at Visit 4, 4 hours ± 30 minutes and 8 hours ± 30 minutes after the end of study drug self-administration. A blood beta hCG pregnancy test is required for women of childbearing potential at Visit 2. The lab tests to be performed are listed in the Table below and are to be performed in both phase II and phase III.

Laboratory Assessments		
Haematology	**Serum chemistry**	**Urine analysis**
• Haematocrit (Hct) • Haemoglobin (Hb) • Mean corpuscular haemoglobin (MCH) • Mean corpuscular haemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood cell (RBC) count • White blood cell (WBC) count with differential	• Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Total bilirubin • Direct bilirubin • Blood Urea Nitrogen (BUN) • Creatinine • eGFR estimated by means of simplified MDRD equation • Potassium • Sodium • Phosphorus • Calcium • Chloride • Glucose • Pregnancy test (beta hCG at Visit 2)	• Appearance • pH • Protein • Glucose • Ketone bodies • Indicators of blood and WBCs • Specific gravity* • Urobilinogen

*Urine specific gravity may decrease because of osmotic diuresis caused by mannitol. The event is to be considered expected.

8.2 SAFETY

The assessment of overall safety consists in recording and evaluating all adverse events, haematological and chemical parameters (see *Section 8.1.4*), and vital signs. The following adverse events are of particular interest in this study:

- Nausea, vomiting, abdominal pain, bloating, thirst, dizziness, sleep disturbance, hypotension
- Acute disruption of electrolyte homeostasis
- Complications of colonoscopy: colonic perforation, bleeding, cardiovascular complications, explosion

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event can be defined as any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. Investigators are to judge the causal relationship of the event with the study intervention as "suspected", "unsuspected" or "unknown".

8.3.3.3 EXPECTEDNESS

The Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the reference safety information.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions will be captured on the appropriate case report form (eCRF). Information to be collected includes event description (a diagnosis and not symptoms should be provided, if possible), time of onset, clinician's assessment of severity, relationship to study drugs, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator will record all reportable events with onset dates occurring any time after informed consent is obtained up to and including the day of colonoscopy. Events will be followed for outcome information until resolution or stabilization, except for those events deemed to be chronic by the Investigator, such as cancer. Lesions detected during colonoscopy (polyps, adenomas, cancer, diverticulosis, hernia, etc.) are not to be considered as AEs.

8.3.5 NON-SERIOUS ADVERSE EVENT REPORTING

All identified non-serious AEs (related and unrelated) must be recorded and described on the eCRF.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Every SAE, regardless of suspected causality, occurring after the subject has provided informed consent up to and including the day of colonoscopy, must be reported to the sponsor immediately but not later than 24 hours after site awareness.

Any SAE experienced after this period should only be reported to the sponsor if the Investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information.

Information about all SAEs will be recorded using the e-safety tool of the eCRF. In case of technical difficulties, SAE notification can be carried out using a paper SAE form and by contacting OPIS, a contract research organization (CRO), via email at all_phv@opis.it or by fax using the following number: +39 0362 633622.

All SAEs will be followed until satisfactory resolution or until the site Investigator deems the event to be chronic. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study sponsor will be responsible for notifying Health Authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

8.3.7 REPORTING OF PREGNANCY

Pregnant women will not be permitted to participate in this study. A negative pregnancy test will be required to enter the study. The Investigator shall report all pregnancy exposures occurring in a female patient within 24 hours to the sponsor using the e-pregnancy tool of the eCRF. In case of technical difficulties, pregnancy notification can be carried out using a paper pregnancy form and by contacting the CRO via email at all_phv@opis.it or by fax using the following number: +39 0362 633622. The Investigator should counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the foetus potentially induced by participation in the study. Monitoring of the subject should continue until conclusion of the pregnancy.

9 STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

The total number of patients to be enrolled is approximately 846; 150 patients (50 in each mannitol dose group) for phase II dose finding, and 696 patients (348 in each treatment group) for the phase III non-inferiority study. The population for phase III will not include the patients who participated in phase II.

Phase II - Dose finding

The sample size is based on the precision of the estimate within each treatment group, i.e. the 95% confidence interval of the proportion of patients in each treatment group with adequate bowel cleansing (BBPS total score ≥ 6, with BBPS ≥2 for each segment).

The table below shows the precision of the estimate for different rates of adequate bowel cleansing with a sample size of 50 patients.

Rates of adequate bowel cleansing (%)	Estimate Precision (%) (i.e. 95% CI*)
75	±12
80	±11
85	±10

* Confidence interval estimated through normal approximation of binomial distribution without continuity correction.

Phase II - Pharmacokinetic sub-study

The expected sample size (10 patients in each dose group) is based on feasibility criteria.

Phase III - non-inferiority

The sample size is based on the proportion of patients with adequate bowel cleansing (BBPS total score ≥ 6, with BBPS ≥ 2 for each segment). When the sample size in each group is 313, a two-group large-sample normal approximation test of difference of proportions with a one-sided 0.025 significance level will have 80% power to reject the null hypothesis that the test preparation is inferior to the standard preparation in favour of the alternative hypothesis that the test proportion is not inferior to the standard preparation (the difference in success proportions, $\pi T - \pi S$, is -0.08 or farther from zero in the same direction), assuming that the expected difference in success proportions is 0 and the proportion of successes in the standard group is 0.85 (the success rate for Moviprep® as reported in Bisschops R. et al., 2019, Choi et al., 2018 and Kwon et al., 2016 varies from 85% to 89%).

A proportion of patients with adequate bowel cleansing 8% lower than the expected 85% for gold standard Moviprep® would give a 77% success rate for mannitol, which falls within the 70-88.5% range reported for PEG-ASC (Repici et al., 2012; Choi et al., 2018; Hassan et al., 2013).

Sample size for two-group test of equivalence in proportions (large equal n's)	
Test significance level, α (one-sided)	0.025
Standard proportion, π_S	0.85
Equivalence limit difference, π_T - π_S, Δ_0	-0.08
Test expected proportion, π_T	0.85
Expected difference, π_T - π_S, Δ_1	0
Power (%)	80
N per group	313

Sample size was computed based on normal approximation of binomial distribution without continuity correction

The non-inferiority margin π_T–π_S = -0.08 corresponds to a relative risk π_T/π_S = 0.906. Should the proportion of successes in the standard group be lower than 0.85, the non-inferiority margin will be adjusted in order to have a relative risk of at least 0.906 (e.g. if the proportion of successes observed in the standard group is 0.80, the non-inferiority margin π_T–π_S will be set equal to = -0.075, corresponding to a relative risk equal to 0.906).

The total sample size (626) is adjusted to 696 patients (348 in each treatment group) considering an expected rate of dropouts and major protocol deviations of about 10% (using Freedman's formula (*Control Clin Trials, 1990*): n'= 100*n/(100-x), where x is the expected percent dropout rate).

The correctness of the assumptions used to compute the sample size for phase III of the study will be re-evaluated at the end of phase II and, if needed, the sample size will be re-estimated.

9.2 RANDOMIZATION

At Visit 3, all eligible subjects will be randomized via eCRF to one of the treatment groups according to the study phase. The Investigator or his/her delegate will confirm that the subject has fulfilled all the inclusion/exclusion criteria in the eCRF. The eCRF will assign a randomization number to the subject, which will be used to link the subject to the treatment and will specify a unique medication number for the package of study treatment to be dispensed to the subject. The subject's randomization number will not be shown in the eCRF: only the medication number will be made available.

For each phase of the study a stratified subject randomization list will be produced in balanced blocks through a validated SAS program.

Phase II – dose finding: the randomization will be stratified by centre and by the presence of constipation (yes/no), defined as the recurrent use of laxatives or Bristol Stool Form Scale (BSFS) < 3 in the two weeks before randomisation.

Phase III – non-inferiority: the randomization will be stratified by centre.

9.3 POPULATIONS FOR ANALYSES

The following populations will be used for the statistical analyses:

- Safety set: all patients who take the study preparation, even only partially. Patients will be analysed according to the study drug dose actually received.
- Modified Safety set: all patients who take the study preparation, even only partially, and who do not meet significant protocol violations that regard inclusion/exclusion criteria. Patients will be analysed according to the study drug dose actually received.
- PK population (only for the pharmacokinetic sub-study): all randomized patients who complete the mannitol treatment and have at least one PK assessment, regardless of the outcome of colonoscopy. Patients will be analysed according to the study drug dose actually received.
- Full Analysis Set (FAS): all randomized patients who take the study preparation, even only partially, undergo the colonoscopy, and have a BBPS available for at least one colon segment after standard washing and air insufflation for luminal distension. According to the Intention to Treat (ITT) principle, patients will be analysed according to the study drug dose assigned at randomization.
- Per protocol (PP): all randomized patients who meet the following criteria:
    - Treatment with the study drug completed.
    - Colonoscopy completed adequately in absence of pathological obstruction that prevents reaching the right colon, including the cecum (i.e. endoscope does not find obstacles other than faecal material) and without acute deterioration of general conditions causing procedure suspension.
    - Bowel cleansing assessment and gas measurement are available for all colon segments after standard washing and air insufflation for luminal distension.
    - No significant protocol violations that regard inclusion/exclusion criteria or that can condition evaluations.

  Patients will be analysed according to the study drug dose actually received.

9.4 STATISTICAL ANALYSES

Continuous data will be summarized with standard descriptive statistics (mean, standard deviation, median, minimum and maximum, 1st and 3rd quartiles). Categorical data will be summarized by frequencies and percentages.

No statistical test will be performed for between-group differences in demographic and baseline features (demographics and medical history).

Medical history and adverse events will be described according to System Organ Classes (SOC) and Preferred Terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) and

will be presented by treatment group. Previous/concomitant medications will be presented by treatment group using the World Health Organization Drug Dictionary (WHO-DD).

All analyses will be performed using SAS® version 9.4

9.4.1 ANALYSIS OF VARIABLES

Phase II - Dose finding

Efficacy

The appropriate mannitol dose to be used in the comparative non-inferiority phase (phase III) will be singled out at the end of dose-finding based on the following criteria:

- 75% or greater rate of adequate bowel cleansing.
- Rate of patients in safe conditions, defined as the absence of potentially dangerous levels of H_2 and CH_4 in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left at the sigmoidal-rectum junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension).
- Clinical judgment based on the caecal intubation rate, the incidence of adverse events, treatment adherence and acceptability (considering ease of use, taste and willingness to reuse the preparation).

Should two or all three doses prove to be equally safe and effective, the lowest dose will be selected for phase III of the study.

Descriptive statistics and Wald 95% CI of the proportion of patients with adequate bowel cleansing will be provided for each dose.

In addition, a logistic regression model will be applied to assess the influence of the two stratification factors (constipation in the two weeks before the start of preparation for colonoscopy and centre) on dose response. A patient is considered a responder if he/she presents adequate bowel cleansing. In case of unbalanced enrolment among centres, a pooling approach will be adopted.

A supportive stepwise logistic regression model will also be applied to assess the influence on dose response of potential prognostic factors (i.e. age and previous unsuccessful bowel cleansing procedures) in addition to the two stratification factors. Based on the results from this model, the need to modify the stratification factors for phase III will be evaluated and the study protocol amended, if needed.

No between-group comparisons will be performed. The decision on the dose to be selected for phase III will be made on the basis of descriptive statistics and corresponding 95% CIs and on the

results of the logistic regression models. Endpoints will be analysed on the PP population. Results from the FAS will be used as supportive.

Caecal intubation rate

Descriptive statistics and Wald 95% CI of the caecal intubation rate will be provided for each dose.

Adherence and acceptability

Descriptive statistics and Wald 95% CIs of the following adherence and acceptability variables will be provided for each dose:

- Adherence
- NRS score for ease of use and taste
- Willingness to reuse the preparation

Phase II - Pharmacokinetic sub-study

The pharmacokinetic parameters (C_{max}, t_{max}, AUC_0-t_{0-t}, $t_{1/2}$) of each dose will be analysed descriptively on the PK population.

Phase III - Non-inferiority

Primary efficacy analysis

The proportion of patients with adequate bowel cleansing (BBPS total score ≥ 6, score ≥ 2 for each segment) during colonoscopy after standard washing and air insufflation for luminal distension will be calculated to evaluate the non-inferiority of the test drug vs the standard drug.

Non-inferiority will be assessed by computing the two-tailed Wald 95% confidence interval (CI) of the difference between the two proportions π_T - π_S. Non-inferiority is met if the 95% CI does not cross the predefined non-inferiority margin Δ = -0.08 and lies entirely to the right of the margin (i.e. non-inferiority will be demonstrated if the lower bound of the two-sided 95% CI of the difference is > -0.08).

The non-inferiority margin π_T–π_S = -0.08 corresponds to a relative risk π_T/π_S = 0.906 when the proportion of successes in the standard group is 0.85. Should the proportion of successes in the standard group be lower than 0.85, the non-inferiority margin will be adjusted in order to have a relative risk of at least 0.906 (e.g. if the proportion of successes observed in the standard group is 0.80, the non-inferiority margin π_T–π_S will be set equal to = -0.075, corresponding to a relative risk equal to 0.906).

If the 95% CI of the difference lies completely to the right of 0, the test treatment can be considered superior to the standard treatment at a 5% significance level.

The Wald method for non-inferiority of proportions will be applied (*Dann RS, 2008)*.

The analysis will be performed on both the FAS and PP populations. Results from both populations will have equal importance.

Secondary efficacy analyses

The analysis of secondary variables will be performed on the FAS. No between-group inferential analysis will be performed. Descriptive statistics and 95% CIs of the between-group differences will be applied on the following variables:

- Number, appearance, size, location and histological classification of neoplastic and inflammatory colorectal lesions detected
- Adenoma detection rate
- Caecal intubation rate
- Ottawa bowel preparation scale

Confidence intervals for proportions will be calculated based on the Wald method.

Adherence and acceptability

The analysis of adherence variables will be performed on the FAS. No between-group inferential analysis will be performed. Descriptive statistics and Wald 95% CIs of the between-group differences will be applied on the following variables:

- Bowel Cleansing Impact review (BOCLIR) scales
- Adherence
- NRS score for ease of use and taste
- Willingness to reuse the preparation

9.4.2 ANALYSIS OF SAFETY

Descriptive statistics both on the Safety set and on the modified Safety set for both phase II and phase III will be performed on:

- Proportion of patients with presence/absence of potentially dangerous levels of H_2 and CH_4 (> 4% Vol and >100% LEL, which is equal to 5% Vol, respectively) in each colon segment during colonoscopy after standard washing and air insufflation for luminal distension.
- H_2, CH_4 and O_2 concentrations, expressed in % Vol, in each colon segment (right, between ileocecal valve and appendix or as close as possible to the ileocecal valve in case of obstacles that prevent reaching the valve; transverse, including flexures; and left, at the sigmoidal-rectum junction, 15-25 cm from anal margin) after standard washing and air insufflation for luminal distension. CH_4 (% LEL) will be converted into % Vol by means of the following formula: (CH_4 in % LEL)*5/100.
- Proportion of patients with adverse events and the number and types of events occurred.

- Proportion of patients with change from baseline (Visit 2) considered clinically significant by the Investigator of haematological and chemical parameters, where clinically significant means that the change causes an additional control or a medical intervention.
- Proportion of patients with change from baseline (Visit 2) considered clinically significant by the Investigator of vital signs (heart rate, systolic and diastolic blood pressure) (phase III only) and proportion of patients with clinically significant change of pulse oximetry and heart rate measured during colonoscopy, as well as systolic and diastolic blood pressure measured immediately prior and after colonoscopy (phase III only), where clinically significant means that the change causes an additional control or a medical intervention. Of note, clinically significant changes of blood pressure measured during colonoscopy will also be reported if considered clinically significant by the Investigator.

The analyses on the modified Safety set will be considered as supportive.

For phase III only, descriptive statistics will be provided on intestinal gas concentrations following the introduction of the colonoscope in the rectum/sigma before standard washing and air insufflation.

9.4.3 PLANNED INTERIM ANALYSES

The final analyses will be performed at the end of phase II and at the end of phase III (no formal interim analysis will be performed). Ongoing data monitoring during phase II will be conducted to properly apply the stopping rule described in *Section 4.1.1*.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, benefits and risks are given to the participant and written documentation of informed consent is required prior to undertaking any study-related procedures.

10.1.1.2CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be approved by the IEC/IRB and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigator, IEC/IRB, Sponsor and regulatory authorities.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance with protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IEC/IRB and/or regulatory authorities.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the sponsor. All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the IEC/IRB, regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IEC/IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the CRO (OPIS) working on behalf of the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Only the study centre will be able to link the study ID number to the patient's identity. The study data entry and study management systems used by clinical sites and by OPIS research staff will be secured and password protected.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Not applicable. All biologic samples will be destroyed following the completion of study-specific assessments indicated in this protocol.

10.1.5 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is compliant with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirements.

The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to GCP, the progress of enrolment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The Investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information. All information on eCRFs must be traceable to these source documents in the patient's file. The Investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

Monitoring standards require full verification for the presence of informed consent, adherence to inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific Monitoring Plan (MP). No information in source documents about the identity of the patients will be disclosed.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

Following written standard operating procedures, monitors will verify that the trial is being conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements.

The investigational site will provide direct access to all trial-related facilities, source data/documents and reports for the monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

Independent audits may be conducted to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the MP. Independent audits may be conducted by the Sponsor to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the MP.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection

Designated Investigator staff will enter the data required by the protocol on the eCRF using fully validated software that conforms to 21 CFR Part 11 and GCP requirements. Designated Investigator site staff will not be given access to the electronic data capture system until they are trained.

Web-based software will be used, and no installation procedure is needed. Each site will be authorized by the administrator to access the eCRF. Each site-qualified personnel will be allowed to access the eCRF by means of a login mask requiring user ID and password and may read, modify, and update only the information previously reported at his or her site and according to their profile. Each page reports site code and subject code.

On-line validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the CRO working on behalf of the sponsor. The Investigator will certify that the data entered on the eCRF are complete and accurate.

After database lock, the Investigator will receive a CD-ROM of subject data for archiving at the investigational site.

Database management and quality control

The CRO (OPIS) working on behalf of the Sponsor will review the data entered on the eCRF by investigational staff for completeness and accuracy and instruct site personnel to make any necessary corrections or additions. The Data Manager will perform the cleaning session by reviewing the warning messages raised by on-line checks and by running post-entry checks by means of validation programs and data listings specific for the study. If clarifications are needed, the Data Manager will raise queries by means of data query forms through the web application. Designated Investigator site staff will be required to respond to queries and the Data Manager will make the correction to the database according to the responses.

Data collection and query flows, as well as the on-line and off-line checks, are detailed in the Data Management Plan and Data Validation documents.

Concomitant medications and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomic Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the MedDRA.

All protocol deviations will be verified and documented, and the database will be locked and made available for data analysis after these actions have been completed and the database has been declared complete and accurate.

10.1.7.2 STUDY RECORDS RETENTION

The Investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (paper and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the study unless the sponsor provides written permission to dispose of them or requires their retention for an additional period because of applicable laws, regulations and/or guidelines. The subjects' medical files will be archived in accordance with the national laws.

10.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol and International Conference on Harmonization Good Clinical Practice (ICH GCP). Noncompliance may be either on the part of the participant, the Investigator, or the study site staff. In case of deviations, corrective actions are to be developed by the site and implemented promptly. It is the responsibility of the site to avoid any protocol deviations and of the site staff and monitors to use continuous vigilance to identify and report deviations. All deviations and relevant actions taken must be properly documented.

10.1.9 INSURANCE

The Sponsor certifies that it has taken out a liability insurance policy covering this clinical trial. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IEC/IRB and/or regulatory authorities.

10.1.10 PUBLICATION AND DATA SHARING POLICY

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor.

This study will ensure that the public has access to the published results of the research.

As the study involves more than one centre, the first publication must be related to data collected from all patients enrolled and analysed under the Sponsor's responsibility. The Investigator shall not publish or communicate data collected at only one centre or part of the centres before the publication of the complete results of the study unless prior written authorization from the Sponsor has been provided.

Enrolment of patients in the study will be competitive. Therefore, pending confirmation from the journal accepting the manuscript, the main publication reporting the results of each phase of the study will include as main authors the names of the Chairman of the study, National Coordinators and Principal Investigators of the five centres enrolling the most patients in each phase of the study. Names of Principal Investigators of all other sites will be mentioned in the full list of participating centres added to the text of the publications.

Any publication and/or communication project regarding the study and/or its results, whether obtained during the study or after the study end, shall be submitted to the Sponsor at least 30 days for a publication and 15 days for an abstract before the planned date of communication and/or submission for a publication. The Sponsor shall make comments on the project within 15 days of receipt of the project for a publication and within 7 days for an abstract. The Investigator who submitted the project shall take the Sponsor's comments into due consideration. Nevertheless, should the Investigator who submitted the project decide not to modify the project according to the Sponsor's comments, he/she shall provide the Sponsor with the grounds for his/her decision in writing.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

AE	Adverse Event
ATC	Anatomic Therapeutic Chemical
BBPS	Boston Bowel Preparation Scale
BfArM	German Federal Institute for Drugs and Medical Devices
BSFS	Bristol Stool Form Scale
BOCLIR	Bowel Cleansing Impact Review
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CRO	Contract Research Organization
eCRF	electronic Case Report Form
ESGE	European Society of Gastrointestinal Endoscopy
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMPD	Investigational Medicinal Product Dossier
IRB	Institutional Review Board
ITT	Intention to Treat
LEL	Lower Explosion Level
MedDRA	Medical Dictionary for Regulatory Activities
MP	Monitoring Plan
NRS	Numeric Rating Scale
OS	Ottawa Scale
PEG	Polyethylene Glycol
PEG ASC	Polyethylene Glycol Ascorbate
PEC-ELS	Polyethylene Glycol and electrolytes
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SoA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
WHO-DD	World Health Organization Drug Dictionary

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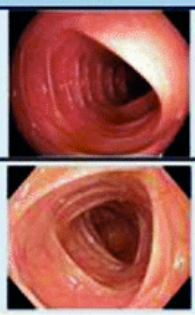
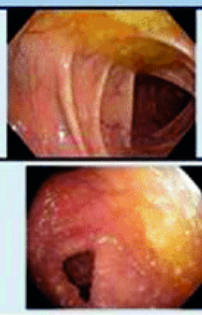
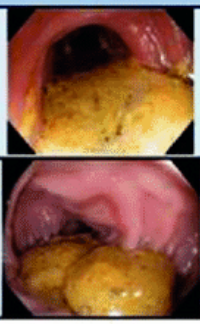
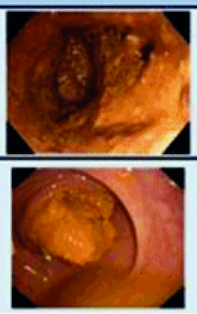
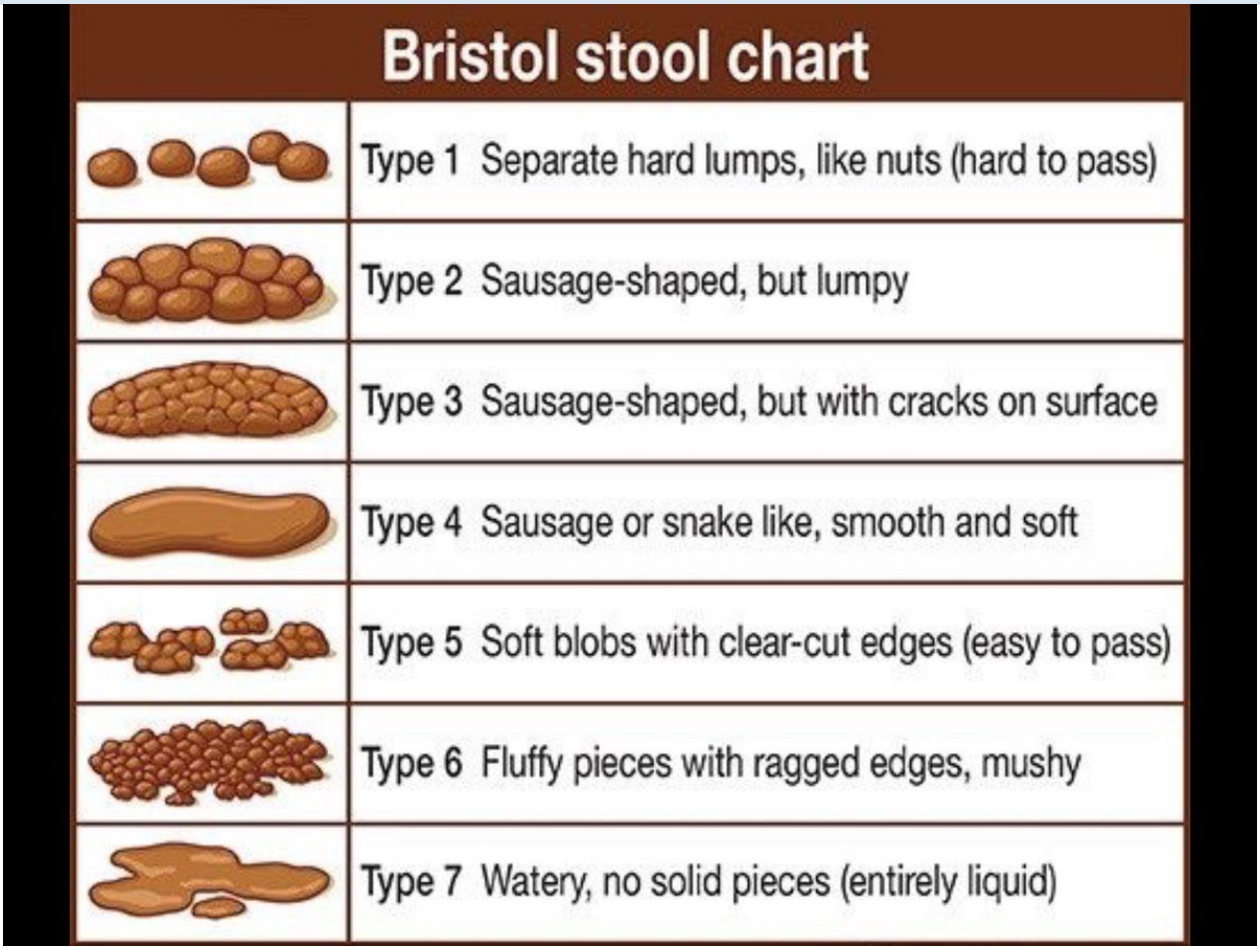
13 APPENDICES

13.1 APPENDIX 1 BOSTON BOWEL PREPARATION SCALE

BBPS		3	2	1	0
3=Excellent 2=Good 1=Poor 0=Inadequate					
LC	☐	☐	☐	☐	☐
TC	☐	☐	☐	☐	☐
RC	☐	☐	☐	☐	☐
BBPS= ☐					

From: Lorenzo-Zúñiga V, Moreno-de-Vega V, Boix J. Preparation for colonoscopy: types of scales and cleaning. Rev. Esp Enferm Dig. 2012; 104: 426-431.)

13.2 APPENDIX 2 BRISTOL STOOL FORM SCALE



13.3 APPENDIX 3 OTTAWA BOWEL PREPARATION SCALE

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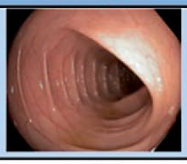
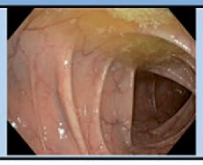
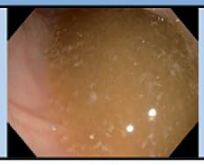
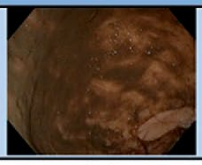
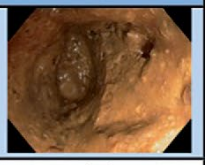
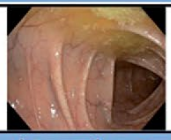
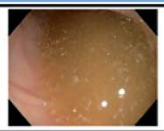
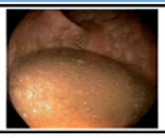
0=Excellent 1=Good 2=Fair 3=Poor 4=Inadequate					
LC ☐	☐	☐	☐	☐	☐
TC ☐	☐	☐	☐	☐	☐
RC ☐	☐	☐	☐	☐	☐

OBPS (B)	0		1		2	
☐		☐		☐		☐

OBPS (A+B) = ☐

From: Lorenzo-Zúñiga V, Moreno-de-Vega V, Boix J. Preparation for colonoscopy: types of scales and cleaning. Rev. Esp Enferm Dig. 2012; 104: 426-431.)