EFFICACY, SAFETY AND TOLERABILITY OF A BOWEL CLEANSING PREPARATION (EZICLEN®/IZINOVA®) IN PAEDIATRIC SUBJECTS UNDERGOING COLONOSCOPY: A PHASE III, MULTICENTRE, RANDOMISED, COMPARATIVE STUDY VERSUS KLEAN-PREP® (PEG-ELECTROLYTES), ADMINISTERED ON THE DAY BEFORE COLONOSCOPY, INVESTIGATOR-BLINDED, NON-INFERIORITY IN ADOLESCENTS OF 12 TO 17 YEARS OF AGE (INCLUSIVE) >40 KG.

STUDY PROTOCOL

STUDY number: F-FR-58800-003

EASYKID
EudraCT number: 2016 002265 60
Final Version 7.0 (including Amendment #6): 02 March 2020

Sponsor's Medically Responsible Person:
PPD
Ipsen Group
65 quai Georges Gorse,
92100 Boulogne-Billancourt, France
Tel: PPD
Fax:

Study Sponsor
Ipsen Pharma SAS
Ipsen Group
65 quai Georges Gorse,
92100 Boulogne-Billancourt, France
Tel: +33 (0)1 58 33 50 00
Fax: +33 (0)1 58 33 50 01

Monitoring Office:
ICTA
11 rue du Bocage
21121 Fontaine-Les-Dijon
FRANCE
Tel: PPD
Fax:

Co-ordinating Investigator:
PPD
Children's Memorial Health Institute
Gastroenterology, Hepatology
& Nutrition Disorders
Al Dzieci Polskich 20
Warszawa 4730
POLAND
Tel:PPD
Fax

Pharmacovigilance/Emergency Contact:
PPD Ipsen Innovation,
ZI de Courtaboeuf - 5 avenue du Canada - 91940 Les Ulis - France
Tel:PPD
Tel:
For SAEs reporting:
Fax: PPD
Email:

INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol [F-FR-58800-003] entitled Efficacy, safety and tolerability of a bowel cleansing preparation (Eziclen®/Izinova®) in paediatric subjects undergoing colonoscopy: a Phase III, multicentre, randomised, comparative study versus Klean-Prep® (PEG-Electrolytes), administered on the day before colonoscopy, investigator-blinded, non-inferiority in adolescents of 12 to 17 years of age (inclusive) >40 kg. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:
TITLE: PRINCIPAL INVESTIGATOR SIGNATURE:

DATE:
OFFICE:

Sponsor's Representative Signature:
NAME: PPD
TITLE: SIGNATURE:

DATE:
OFFICE: Ipsen Pharma SAS
Medical Department
Medical Affairs Consumer HealthCare
65 quai Georges Gorse
92100 Boulogne-Billancourt, France

[COORDINATING INVESTIGATOR'S AGREEMENT]

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol [number F-FR-58800-003] entitled Efficacy, safety and tolerability of a bowel cleansing preparation (Eziclen®/Izinova®) in paediatric subjects undergoing colonoscopy: a phase III, multicentre, randomised, comparative study versus Klean-Prep® (PEG-Electrolytes), administered on the day before colonoscopy, investigator-blinded, non-inferiority in adolescents of 12 to 17 years of age (inclusive) >40 kg. I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: PPD

TITLE: COORDINATING INVESTIGATOR SIGNATURE:

DATE:

OFFICE: Children's Memorial Health Institute
Gastroenterology, Hepatology & Nutrition Disorders
Al Dzieci Polskich 20
Warszawa 4730
POLAND

SUMMARY OF CHANGES

The current version of the protocol was released on 02 March 2020 and includes all amendments. Amendment forms were prepared and are provided in Appendix 1 to Appendix 6 (Table 1).

Table 1 List of Protocol Amendments

Amendment	Release date	Amendment form
1	13 January 2017	Appendix 1
2	23 March 2017	Appendix 2
3	17 July 2017	Appendix 3
4	16 March 2018	Appendix 4
5	26 July 2018	Appendix 5
6	02 March 2020	Appendix 6

SYNOPSIS

Name of sponsor/company: IPSEN GROUP	
Name of finished product: Eziclen®/Izinova® **Name of active ingredients**: sodium sulphate anhydrous, potassium sulphate, magnesium sulphate heptahydrate	
Title of study: Efficacy, safety and tolerability of a bowel cleansing preparation (Eziclen/Izinova®) in paediatric subjects undergoing colonoscopy: a Phase III, multicentre, randomised, comparative versus Klean-Prep® (PEG-Electrolytes), administered on the day before colonoscopy, investigator-blinded, non-inferiority study in adolescents of 12 to 17 years of age (inclusive) >40 kg. **Study number**: F-FR-58800-003	
Number of planned centres: around 25 centres	
Planned study period: From Q4 2017 to Q2 2020	**Phase of development**: Phase III

Objectives:

Primary objective:

To demonstrate that Eziclen®/Izinova®, an osmotic sulphate-based laxative preparation given on the day before colonoscopy has non-inferior efficacy to Klean-Prep® (polyethylene glycol (PEG)-electrolytes) on colon cleansing in adolescents aged 12 to 17 years (inclusive) with a body weight >40 kg, scheduled to undergo a colonoscopy for a routinely accepted diagnostic indication

Secondary objectives:

- To compare efficacy of Eziclen®/Izinova® versus Klean-Prep® on overall and segmental cleansing and colonoscopy quality indicators
- To assess compliance with preparation administration in both study arms
- To compare safety, acceptability and tolerability of Eziclen®/Izinova® versus Klean-Prep®

Methodology:

- Multicentre, investigator-blinded, randomised Phase III comparative study
- In adolescents (male and female) >40 kg with routine indication for colonoscopy
- Eziclen®/Izinova® solution: oral administration at 3/4 adult dose versus Klean-Prep® (70 mL/kg, maximum 4000 mL), both administered as 1-day regimen on the evening before colonoscopy
- Subjects will be hospitalised from baseline (Visit 1, Day 1) to completion of colonoscopy (Visit 2, Day 2)
- The maximum duration of the study for each subject will be 47 days: Baseline (Visit 1) and treatment administration on Day 1, colonoscopy (Visit 2) on Day 2, phone contact (Visit 3) at Day 4 ±1, 30-day follow-up at the final visit (Visit 4) on Day 32 (-5/+15, i.e. ranging from Day 27 to Day 47)

Number of subjects planned:

A total of 250 male and female adolescents will be randomised in order to have 240 evaluable subjects.

Diagnosis and criteria for inclusion:

Inclusion criteria:

Subject MUST satisfy all of the following entry criteria before being allowed to participate in the study:

(1) Provision of signed informed consent form (ICF) to participate in the study obtained from the adolescent's parent(s)/ legal representative and a signed assent form from the adolescent according to local law

(2) Male or female subjects between 12 to 17 years of age (inclusive)

(3) Body weight more than 40 kg

(4) Female of childbearing potential must have a negative pregnancy test

(5) If female, and of child-bearing potential, subject must use an acceptable form of birth control (hormonal birth control, intrauterine device (IUD), double-barrier method, or depot contraceptive)

(6) Routinely accepted indication for undergoing colonoscopy, including but not limited to polyposis coli diagnosis or surveillance, gastrointestinal bleeding, unexplained diarrhoea or constipation, surveillance of inflammatory bowel disease or confirmation of mucosal healing, abdominal pain, abnormal endosonography or manometry, anaemia of unknown aetiology, cancer surveillance

(7) In the investigator's judgment, the parent(s)/legal representative are/is mentally competent to provide informed consent for the subject to participate in the study

(8) In the investigator's judgement, subject is able and willing to follow study procedures including drug administration and response to questionnaires

Exclusion criteria:

If any of the following apply, the subject MUST NOT enter/continue in the study:

(1) Subject with known or suspected ileus, gastrointestinal obstruction, gastric retention (gastroparesis), rectal impaction, toxic colitis, severe ulcerative colitis or toxic megacolon, advanced carcinoma, swallowing disorders

(2) Subject with known or suspected inflammatory bowel disease (Crohn's disease, ulcerative colitis) in moderate to severe active phase defined by PCDAI >30 (Crohn's disease) or PUCAI >34 (ulcerative colitis)

(3) Subject with bowel perforation or increased risk of bowel perforation, including connective tissue disorders or recent bowel surgery

(4) Subject with previous significant gastrointestinal surgery (e.g. colostomy, colectomy, gastric bypass, stomach stapling)

(5) Subject with uncontrolled pre-existing electrolyte abnormalities, or with electrolyte abnormalities based on Visit 1 laboratory results such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalaemia, hypocalcaemia, uncorrected dehydration, or secondary to the use of medications such as diuretics or angiotensin converting enzyme (ACE) inhibitors judged clinically significant by the investigator

(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2 as calculated by using the Schwartz bedside equation* [Schwartz et al, 2009]**), liver (ascites, Child-Pugh C), cardiac insufficiency (including congestive heart failure all grades) or hyperuricemia

*The estimated GFR will be calculated in patients with elevated creatinine at baseline.

** Schwartz GJ and Work DF. Measurement and Estimation of GFR in Children and Adolescents. Clin J Am Soc Nephrol. 2009; 4: 1832–1843

(7) Female subject who is pregnant or lactating

(8) Subject who has participated in another investigational drug treatment within the last 90 days before the first study visit

(9) Subject with phenylketonuria

(10) Subject with history of asthma or hypersensitivity to any ingredient of either drug product

(11) Subject for whom intake of substances likely to affect gastrointestinal motility or urinary flow rate is required

(12) Subject with requirement to take any other oral medication within 3 hours of starting the bowel preparation, as this may impact medication absorption

(13) Subject with tendency for nausea and/or vomiting

(14) Subject with impaired consciousness that predisposes them to pulmonary aspiration or who have known swallowing disorders

(15) Subject with history of major medical/psychiatric conditions that, in the judgment of the investigator, would compromise safety in the study

(16) Subject with mental or psychiatric condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude

(17) Subject with a condition that, in the opinion of the investigator, might increase the risk to the subject or decrease the chance of obtaining satisfactory data needed to achieve the objectives of the study

(18) Subject who has previous enrolment in this study or concomitant enrolment in other clinical studies

Test product, dose, mode of administration:

In this single-blinded study, to ensure an unbiased evaluation of the study preparations, the colonoscopist will not be allowed to perform any study drug related activities (randomisation, drug dispensing, return and accountability, acceptability, tolerability and review of subject's leaflet/questionnaires). Any failure to maintain blinding of the treatment to the colonoscopist will be documented as a protocol violation. Subjects and caregivers will be instructed not to discuss their study preparation with the colonoscopist or any staff member other than with the study nurse who will collect the questionnaires.

Eziclen®/Izinova®:

The bowel cleansing preparation will be given orally on the evening of the day before colonoscopy. The total dose administered is 3/4 of the adult dose (product dispensed).

Evening before the procedure (e.g., 6:00 pm):

The two bottles of Eziclen®/Izinova® (180 mL X 2 concentrate sulphate salt solution) are to be diluted up to 1000 mL with water, using a 1000 mL graduated measuring glass. A total of 250 mL (1/4) of the preparation will be discarded. The remaining 750 mL of the preparation (3/4 adult dose) will be divided in two equal portions. The first portion of 375 mL will be drunk slowly in ½ to 1 hour, followed by an additional 750 mL of water over the next hour. The total ingested volume is 1125 mL.

Approximately 2 hours after the start of drinking the first portion (e.g., 8:00 pm):

The second 375 mL portion of the Eziclen®/Izinova® preparation will be drunk slowly in ½ to 1 hour followed by additional 750 mL of water over the next hour. The total ingested volume is 1125 mL.

The total volume of preparation drunk is 750 mL, with an additional 1500 mL of water, for a total of 2250 mL. If a subject experiences difficulty in drinking the bowel cleansing preparation, a nasogastric tube will be placed, the rate of administration should not exceed 30 mL/kg/hour.

Reference therapy, dose and mode of administration:

Comparator compound: Klean-Prep® (Powder for Oral Solution):

The comparator, Klean-Prep® is a powder for oral solution packaged in 4 sachets. Each treatment pack is composed of 4 sachets with a total of 69 g of the product (powder for oral solution) included in each sachet. The complete dose of the preparation will be administered on the day prior colonoscopy, in the evening.

Evening before the procedure (e.g., 6:00 pm)

The 4 sachets are to be diluted. Each sachet is diluted in one litre of water.

The dosage will be 70 mL/kg (which corresponds to the approved posology for that class of age and/or weight). The maximum volume administered will be 4000 mL.

The whole solution will be administered in two half doses (1 litre per hour) with a 1-hour pause between the two half doses. If a subject experiences difficulty in drinking the bowel cleansing preparation, a nasogastric tube will be placed, the rate of administration should not exceed 30 mL/kg/hour.

Other treatments: rescue treatment

Only if clear discharge has not been obtained 1 hour prior to procedure:

Normal saline enema, 1000 mL; repeated until clear discharge is obtained. Sodium phosphate enemas are not to be used.

Duration of treatment:

Subject participation in this study may last up to 47 days.

Criteria for evaluation:

Efficacy:

Primary Endpoints and Evaluations:

Non-inferiority of Eziclen®/Izinova® versus Klean-Prep® in the cleansing of the colon:

Blinded overall assessment of preparation efficacy (Cleansing Score) as determined by the colonoscopist upon completion of the examination, based on a 4-point scale:

Score	Grade	Description
4	Excellent	No more than small bits of adherent faeces/fluid
3	Good	Small amounts of faeces or fluid not interfering with examination
2	Fair	Enough faeces or fluid to prevent a completely reliable examination
1	Poor	Large amounts of faecal residue, additional cleansing required

Only perfect preparations graded as excellent (4) or good (3), which allow full, reliable examination of the mucosa, will be considered as successful.

Primary efficacy will be assessed on the basis of preparation success or failure.

Secondary Endpoints and Evaluations:

- Need to place a nasogastric tube to complete preparation
- Time to clear effluent (from first intake of preparation), as reported by the subject
- Need for rescue treatment (saline enema) because of inadequate preparation
- Cleansing Scores assessed by the 4-point scale (poor, fair, good, excellent)
- Overall and segmental Cleansing Scores assessed by Boston Bowel Preparation Scale (BBPS)
- Duration of intubation (from colonoscope introduction to caecal intubation)
- Duration of examination, measured by colonoscope withdrawal time from caecum
- Procedure documented as completed (procedures that reached the caecum)
- Treatment compliance: volumes of fluids measured by the caregiver and reported in the treatment questionnaire of subject's leaflet during treatment administration
- Treatment acceptability, assessed by Treatment Acceptability Questionnaire completed by caregiver or subject at the time of intake using a 5-point scale questionnaire to be filled in by the subject immediately after dosing

Very badly accepted/unacceptable	Subject showed great displeasure, compromising use of formulation
Badly but accepted	Subject showed displeasure with dosing but could be coaxed to take complete dose
Neither good nor bad	Subject showed no apparent displeasure and with little effort was coaxed to take complete dose
Well accepted	Subject appeared to enjoy the formulation and with little coaxing ingested complete dose
Very well accepted	Subject appeared eager and ingested complete without special coaxing

Safety and tolerability:

- Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy)
- Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and

nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms • Description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage • Vital signs including body weight and physical examination • Laboratory data: serum and urinary biochemistry: • Visit 1 • Day 2 (colonoscopy) • Visit 4
Statistical Methods: The primary aim of the study is to show that Eziclen®/Izinova® is not inferior to Klean-Prep® in the proportion of subjects with successful colon cleansing. A non-inferiority margin of 15% has been selected for consistency with other studies in colon cleansing preparations. Therefore assuming a success rate (excellent or good response) of 85% in both the Eziclen®/Izinova® and Klean-Prep® groups, a one-sided alpha of 0.025 and 90% power, 120 subjects are required per treatment group. Assuming a rate of dropout / non-compliance to protocol of 4% based on previous studies and taking into account that subjects will be hospitalised), 125 subjects will be randomised in each treatment group, i.e. 250 subjects in total. Enrolment will be completed once 250 subjects have been randomised. The primary endpoint of treatment success will be tested sequentially (hierarchical structure) with the first test being non-inferiority test based upon the treatment difference. A rejection of the null hypothesis will trigger superiority testing based upon the treatment difference. The two hypothesis tests are hierarchically structured so that the second test (superiority) will only be considered if the first test (non-inferiority) is rejected. The superiority test is powered to detect an absolute difference of 18%. There is no alpha adjustment for the second test as a result of the hierarchical testing. The primary efficacy analysis will be based on the modified Intention To Treat (mITT) population and will include all randomised subjects who received even a partial dose of study treatment and produced a primary efficacy assessment. Subjects who do not undergo colonoscopy because of inadequate preparation or preparation-related AEs will be considered as failures. In addition, robustness of primary efficacy results will be assessed by repeating the primary analysis on the Per Protocol (PP) population and will include all subjects in the ITT population, who have undergone the colonoscopy procedure and for whom no major protocol violations/deviations occurred. The proportion of subjects with successful colon cleansing (graded as excellent or good) will be summarised along with the 95% confidence interval (CI) using the standard Wald asymptotic CI. The primary efficacy endpoint will be analysed using a logistic regression model including country as stratification variable, the interaction between country and

treatment will be also investigated. The formal hypothesis test result (p-value) for treatment difference will be presented together with a two-sided 95% CI for the difference in success rates. The non-inferiority will be demonstrated if the lower limit of the 95% CI of that difference is higher than -15%.

The schedule of procedures and assessments during the study is summarised below.

Study Procedures and Assessments

Study Period	**Baseline/ Treatment**	**Colonoscopy**	**Phone contact**	**End of Study (or in case of Early Withdrawal*)**
Visit	**1**	**2**	**3**	**4**
Day	**Day 1**	**Day 2**	**Day 4**	**Day 32**
Window			±1	**-5/+15 i.e. Day 27 to Day 47**
Eligibility Criteria	X			
Demographic Data	X			
Blood Pregnancy Test [a]	X			
Informed Consent (parent(s) or legal representative)	X			
Assent (subject)	X			
Medical and Surgical History	X			
Indication(s) for Colonoscopy	X			
Prior and Concomitant Medication [b]	X	X		X
Prior and Concomitant Non-Drug Therapy [b]	X	X		X
AEs [c]	X[d]	X	X[e]	X
Physical Examination	X			X
Vital Signs (Temperature, blood pressure (BP) and heart rate (HR)	X	X		X
Body Weight and height[f]	X	X		X
Blood sample collection [g], [h]	X[i]	X[j]		X
Urine sample collection[k]	X	X		X
Blood and urine sulphates[l]	X	X[j]		X
RANDOMISATION [m]	**X**			
Study treatment dispensation (with explanation of treatment administration)	X			
Subject/caregiver leaflet dispensation by study nurse (with explanation of questionnaires including compliance measurement)	X			
Subject takes treatment preparation	X			

Completion of leaflet questionnaires by subject/ caregiver/ nurse				
• Treatment / Compliance	X			
• Treatment Acceptability	X			
• Symptom Scale (Tolerability)	X			
Collection of leaflet questionnaires by study nurse		X		
Drug accountability/ study administration compliance by unblinded site member		X		
Colonoscopy assessment [n]		X		
Subject status at the end of the visit	X	X	X	X

*Early withdrawal will be anytime from Visit 1

[a] If applicable. Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.

[b] Prior and concomitant medication and non-drug therapy will from 7 days before baseline and for any action taken by the investigator

[c] AEs will be actively collected by the investigator and subjects will be instructed to contact the investigator if they experience any AEs

[d] At baseline, AEs will be collected from the date of informed consent and assent signature

[e] The investigator will contact the subject by phone on Day 4±1 to collect data on potential AEs

[f] Height will be measured at Baseline only

[g] Local laboratory (blood): biochemistry including: anion gap, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactic dehydrogenase (LDH), gamma-glutamyl transferase (GGT), total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, C reactive protein (CRP), uric acid, creatinine clearance (calculated GFR), osmolality

[h] Laboratory assessments performed within 10 days or less prior to inclusion may be used to determine eligibility upon investigator agreement.

[i] Additional local laboratory haematology: complete blood count (CBC), international normalised ratio (INR).

[j] Blood sampling during anaesthesia

[k] Local laboratory urine analysis (by dipstick), microscopic examination

[l] Collection of blood and urine sample for central laboratory sulphate dosage

[m] Randomisation if satisfactory biochemistry results

[n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, diagnosis/findings

Subject's Leaflet Collected Information

	During/after Dose 1 Day 1	During/after Dose 2 Day 1
Treatment/Compliance Questionnaire[a]	X	X
Treatment Acceptability Questionnaire	X	X
Symptom Scale (Tolerability)	X	X
Information about time to bowel movement and time to first clear watery stool.		X

a Treatment/Compliance questionnaire will collect information about: preparation of treatment, treatment intakes (recording of residual volumes, start/end times) for Eziclen®/Izinova® or Klean-Prep®.

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LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BBPS	Boston Bowel Preparation Scale
BP	Blood pressure
CA	Competent Authorities
CBC	Complete blood count
CI	Confidence interval
CMC-SC	Chemistry, Manufacturing and Control Supply Chain
CMH	Cochran-Mantel-Hænszel
CPK	Creatine phosphokinase
CRC	Colorectal cancer
CRO	Contract research organisation
CRP	C reactive protein
CSR	Clinical study report
D	Day
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
ELS	electrolyte lavage solution
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
HR	Heart rate
IB	Investigator’s brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form

ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IMP	Investigational medicinal product
INR	International normalised ratio
IRB	Institutional review board
ITT	Intention to treat
IUD	Intrauterine device
LC	Left colon
LDH	Lactic dehydrogenase
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to treat
PEG	polyethylene glycol
PDD	Protocol Deviation Document
PI	Package insert
PP	Per protocol
RBC	Red blood cell
RC	Right colon
SAE	Serious adverse event
SAP	Statistical and analysis plan
SAS®	Statistical Analysis System®
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TC	Transverse colon
TEAE	Treatment emergent adverse event
TMF	Trial master file
US	United States
WBC	White blood cell
WHO	World Health Organisation

1 BACKGROUND INFORMATION

1.1 Introduction

Bowel cleansing is a procedure used before bowel visualisation (colonoscopy, videocapsule, radiology). Colonoscopy is considered to be the gold standard investigation for assessing the colonic mucosa. In adult patients, this bowel visualisation procedure is not only used for screening for colorectal cancer (CRC), but also for diagnosis of colonic diseases (such as inflammatory bowel disease (IBD), ulcers, diverticula), investigation of abdominal pain, unexplained anorectal haemorrhage or diarrhoea, confirmation of abnormalities revealed by other radiological examinations and performing colorectal surgery, such as polypectomy or mucosectomy. In the paediatric setting, the indications for colonoscopy are not the same as in adults and vary depending on the age group considered. Indications include diagnosis and surveillance of IBD including documentation of mucosal healing, exploration of rectal bleeding, chronic diarrhoea, anaemia, abdominal pain, diagnosis and surveillance of polyposis coli syndromes, failure to thrive or weight loss, rejection of intestinal transplant and follow-up of colorectal diseases [1].

As colonoscopy is conducted under anaesthesia in paediatric patients, inadequate preparation not allowing clear visualisation of the mucosa is even less acceptable than in the adult patient setting [2].

A wide variety of preparations are used in paediatrics (excluding sodium phosphates preparations) but there is no standard bowel cleansing regimen in children. Safety and effectiveness of large-volume polyethylene glycol-based solutions have been shown. However, these preparations are often poorly tolerated due to the salty taste and the large volume to be ingested over a relatively short period for a successful colonoscopy preparation. A number of bowel preparation regimens are used, but compliance is often poor and results unsatisfactory. Indeed, as in adults, reports of inadequate preparations involve up to one third of the patients, leading to extended procedure time, incomplete examination, or need for repeat procedure [1].

Eziclen®/Izinova® is a hyperosmotic bowel preparation, composed of sodium sulphate anhydrous, potassium sulphate and magnesium sulphate heptahydrate, indicated for cleansing of the colon as a preparation for colonoscopy in adults only. It was developed in the United States (US) by Braintree Laboratories, and has been marketed in the US since 2010 under the trade name of SUPREP®. In Europe, it was approved by the European Medicines Agency (EMA) in 2013 and is marketed under the trade name Eziclen® or Izinova®. The current study is the second study being conducted as part of the Paediatric Investigational Plan for Eziclen®/Izinova®.

The pivotal studies demonstrating the safety and efficacy of Eziclen®/Izinova® in adults are summarised in Section 1.3.

Klean-Prep®, the comparator, is a Macrogol-based isosmotic laxative containing 59.000 g macrogol 3350, 5.685 g anhydrous sodium sulphate, 1.685 g sodium bicarbonate, 1.465 g sodium chloride, and 0.7425 g potassium chloride. The compound is approved for use in adults in many European countries, and in children in some European countries including France, the Netherlands and the United Kingdom.

1.2 Name and Description of Investigational Medicinal Product

Eziclen®/Izinova® is a hyperosmotic laxative preparation composed of sulphate salts of sodium, potassium and magnesium, the major constituent being sodium sulphate (73%). The mechanism of action of Eziclen®/Izinova® relies primarily on the limited capacity of the gastrointestinal system to absorb sulphate. The absorption of sulphate in the gastrointestinal tract follows a saturable active transport process with the kidneys as the primary pathway for excretion of absorbed sulphate [1, 3]. The osmotic effect of unabsorbed sulphate anions and the associated cations draws water into the intestines, increasing the water content of the stool and causing watery diarrhoea, which leads to effective bowel cleansing. Absorption studies with very large amounts of sodium sulfate (8 g anhydrous sodium sulphate) demonstrated incomplete absorption, which was associated with severe diarrhoea [4].

A more detailed description of the product is given in Section 3.4.

1.3 Findings from Nonclinical and Clinical Studies

Two phase III studies were conducted in adults comparing Eziclen®/Izinova® to a Food and Drug Administration (FDA) approved preparation polyethylene glycol (PEG) + ascorbic acid [5]. The BLI800-301 Study evaluated Eziclen®/Izinova® as a 1-day preparation, completed on the day prior to colonoscopy. The BLI800-302 Study utilised a 2-day (or “split-dose”) regimen in which half the preparation was taken the evening prior to colonoscopy, and the remaining half completed on the morning of the procedure. It should be noted that the split dose preparation is not the favoured mode of administration in children as anaesthesia guidelines require 6 hours of fasting prior to colonoscopy in the paediatric setting.

The primary efficacy analysis in both phase III studies supported the conclusion that Eziclen®/Izinova® is equivalent to PEG + ascorbic acid with respect to cleansing efficacy (cumulative data shown below in Table 2).

Table 2 Primary Efficacy Responder Analysis - BLI800-301/302 Studies

Responder[a]	Eziclen®/Izinova® n (%)	PEG + ascorbic acid n (%)	95% CI	p[b]	p[c]
All Patients (n)	375	376			
Success	334 (89.5%)	330 (87.8%)	-2.8, 6.3	0.410	<0.001
Fail	39 (10.5%)	46 (12.2%)			
301 Patients (n)	194	193			
Success	159 (82.4%)	155 (80.3%)	-5.7, 9.8	0.614	<0.001
Fail	34 (17.6%)	38 (19.7%)			
302 Patients (n)	181	183			
Success	175 (97.2%)	175 (95.6%)	-2.2, 5.4	0.391	<0.001
Fail	5 (2.8%)	8 (4.4%)			

a A successful treatment is defined as bowel cleansing graded either excellent or good (grading score = 3 or 4) by the blinded colonoscopist

b p-value for the difference between treatments

c p-value for the non-inferiority hypothesis using an equivalence margin of 15%

Adverse events (AEs) were also evaluated in the Phase III studies. The only treatment emergent AE category with a frequency greater than 3% was gastrointestinal (Eziclen®/Izinova®=4.5% and PEG+ascorbic acid=4.3%). The expected symptoms of nausea and vomiting were the most frequent (1.3% each) within the gastrointestinal category. There was no difference between Eziclen®/Izinova® and PEG+ascorbic acid in the frequency of any treatment-emergent adverse events (TEAEs), including those that were gastrointestinal in origin. No clinically significant differences between groups were seen in laboratory testing of serum chemistry and haematology. At the 1-month follow-up visit, no change in serum creatinine was observed for Eziclen®/Izinova® patients.

The first study in the Paediatric Investigation Plan was a phase II study (BLI800-501) comparing two split-dose regimens of Eziclen®/Izinova® bowel preparation in paediatric subjects aged 12 – 17 years, who underwent colonoscopy for a routinely accepted indication. The FDA approved adult dose of Eziclen®/Izinova® (two 6-ounce doses, i.e. 180 mL) was compared to a lower volume dose (corresponding to a 3/4 adult dose or two 4.5-ounce doses i.e. 135 mL) to evaluate differences in safety, efficacy and tolerance. A total of 29 subjects were enrolled and took the bowel preparation (16 subjects from the 6-ounce group, 13 subjects from the 4.5-ounce group).

The primary efficacy variable for the study was the proportion of “successful” preparations for colonoscopy (rated as “good” or “excellent” by the colonoscopist). Secondary measures included segmental cleansing and accepted quality indicators (adequate preparation, caecal intubation). There was no difference in preparation success between the two Eziclen®/Izinova® dose groups, with 81% of subjects having a successful preparation in the 6-ounce group, and 83% in the 4.5-ounce group. Adequate preparations were achieved in approximately 86% of subjects (88% in the 6-ounce group, 83% in the 4.5-ounce group). These efficacy rates are lower than those reported using Eziclen®/Izinova® in adult clinical studies [5, 6], but comparable to evening only regimens [5, 7]. The 4.5-ounce dose group had more excellent preparations and less residual stool and fluid segmentally, although these differences did not reach statistical significance (except for fluid in the sigmoid colon/rectum), likely due to the small sample size.

CCI

The goal of the current study is to compare the safety, efficacy and tolerability of Eziclen®/Izinova® (4.5-ounce dose regimen, 3/4 adult dose) in adolescents undergoing colonoscopy compared to a standard PEG- electrolyte lavage solution (ELS) preparation approved in paediatric subjects (Klean-Prep®).

Further details of Eziclen®/Izinova® may be found in the investigator's brochure (IB) [8].

1.4 Known and Potential Risks and Benefits to Human Subjects

Eziclen®/Izinova® is an osmotic low volume, sulphate-based bowel cleansing solution, whose absorption in the gut is limited, thus preserving renal function. Sulphate salts do not alter the normal balance of serum calcium salts. In the nonclinical toxicology and human pharmacology studies, there was no evidence of urinary calcium precipitation [9]. The absorption of magnesium occurs by both an unsaturable passive and saturable active transport systems [10]. Thus, the fractional absorption of magnesium is inversely proportional to the amount ingested. With the quantities present in Eziclen®/Izinova® formulation, the relative absorption of sulphates and magnesium is low. On the basis of serum magnesium measurements, no subject in the Eziclen®/Izinova® clinical phase I and II studies developed hypermagnesaemia.

In adult patients, the overall safety profile of Eziclen®/Izinova® was favourable and the preparation was well tolerated. The safety profile of Eziclen®/Izinova® is similar to that of PEG preparations, the gold standard in this indication. As a result of lower volume of solution

to be ingested, patient willingness to undergo and complete a bowel cleansing regimen prior to any procedure requiring a clean bowel may be improved. The benefit-risk assessment of the compound as a bowel cleansing agent prior to colonoscopy can thus be considered favourable in its indication in the adult patient.

Eziclen®/Izinova® has demonstrated its efficacy in adult patients in three randomised controlled phase III studies and two phase IV studies. Eziclen®/Izinova® studies reported an excellent or good quality of bowel preparation in over 90% of patients (pooled data, 1-day and split-dose). In comparison with other agents, it has been shown to be non-inferior and equivalent to PEG+ascorbic acid when administered as a 1-day or a split-dose regimen [5]. Split-dose Eziclen®/Izinova® was superior to 1-day sulphate free PEG (4 L), although this may reflect differences in the dosing regimen rather than differences between the preparations [6]. In the phase IV studies, a split-dose regimen of Eziclen®/Izinova® was formally demonstrated to be superior in its efficacy to a sodium picosulphate plus magnesium citrate split-dose regimen and to either Eziclen®/Izinova® or PEG+Electrolytes 4L same-day regimens [11]. The Eziclen®/Izinova® same-day regimen was equivalent to PEG+electrolytes. Compliance, as measured by completion of the entire preparation, observed with Eziclen®/Izinova® was high: ≥97% for split-dose and ≥93% for 1-day administration. The efficacy of Eziclen®/Izinova® observed in the elderly population was similar to that in younger adults.

Additional information regarding risks and benefits to human subjects may be found in the IB for Eziclen®/Izinova® [8]. For Klean-prep®, refer to the summary of product characteristics (SmPC) [12].

1.5 Selection of Investigational Medicinal Products and Dosages

The dosages to be evaluated in this investigator-blind study (i.e. 750 mL of Eziclen®/Izinova® solution + 1500 mL of water the day before colonoscopy) were selected on the basis of studies conducted in adults and a study conducted in children aged 12 to less than 18 years (Study BLI800-501 (Efficacy and tolerability of a bowel cleansing preparation in paediatric subjects undergoing colonoscopy)).

A more detailed description of administration procedures is given in Section 6.1.

1.6 Compliance Statement

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented.

The study will also be conducted in compliance with the FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures and FDA, Guidance for Industry (Computerised Systems Used in Clinical Trials), a regulation which provides criteria for acceptance by the FDA of electronic records, e-signatures and hand-written signatures executed to electronic records as equivalent to paper records and hand-written signatures on paper.

In addition, the study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written informed consent form (ICF), assent form, any consent or assent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they

comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

1.7 Population to Be Studied

The study will enrol adolescents aged 12 to 17 years (inclusive), with body weight >40 kg, scheduled to undergo colonoscopy for a routine indication.

2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

2.1 Purpose of the Study

The purpose of the present study is to compare the efficacy, safety and tolerability of Eziclen®/Izinova® to those of Klean-Prep® in adolescents aged 12 to 17 years (inclusive) with body weight >40 kg scheduled to undergo a colonoscopy for a routinely accepted indication.

2.2 Study Objectives

2.2.1 Primary Objective

The primary objective of the study is to demonstrate that Eziclen®/Izinova®, an osmotic sulphate-based laxative preparation given on the day before colonoscopy has non-inferior efficacy to Klean-Prep® (PEG-electrolytes) on colon cleansing in adolescents aged 12 to 17 years (inclusive) with a body weight >40 kg, scheduled to undergo a colonoscopy for a routinely accepted diagnostic indication.

2.2.2 Secondary Objectives

The secondary objectives of the study are as follows:

- To compare efficacy of Eziclen®/Izinova® versus Klean-Prep® on overall and segmental cleansing and colonoscopy quality indicators
- To assess compliance with preparation administration in both study arms
- To compare safety, acceptability and tolerability of Eziclen®/Izinova® versus Klean-Prep®

3 STUDY DESIGN

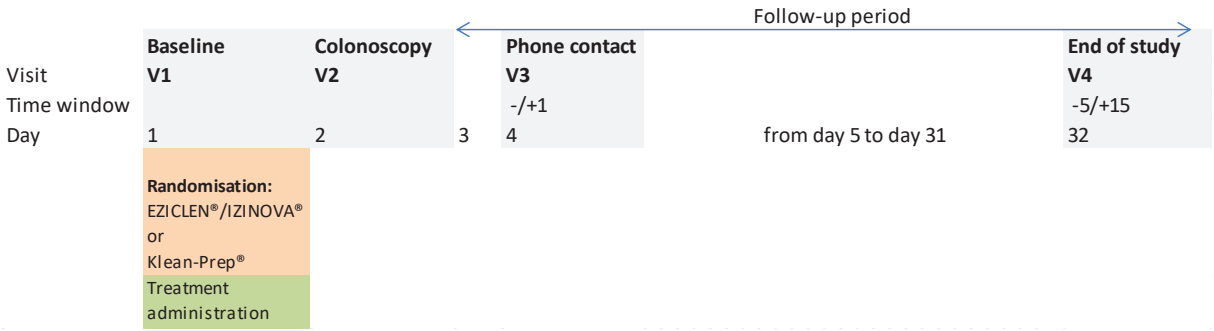
3.1 General Design and Study Schema

This is a multicentre, investigator-blinded, randomised phase III comparative study conducted in adolescents (male and female) >40 kg scheduled to undergo colonoscopy. It is planned to enrol subjects from around 25 centres. Subjects will be randomised in two parallel arms to receive either Eziclen®/Izinova® or Klean-Prep®. Efficacy, safety and tolerability will be assessed. Eziclen®/Izinova® solution will be orally administered at 3/4 adult dose. Its efficacy will be compared to Klean-Prep® (70 mL/kg). Both solutions will be administered as a 1-day regimen on the evening before colonoscopy. A total of 250 male or female subjects aged 12 to 17 years (inclusive) scheduled to undergo colonoscopy will be randomised in this study in order to have 240 evaluable subjects. The maximum duration of the study for each subject will be 47 days:

- Enrolment and Baseline visit at Day 1
- Treatment (Eziclen®/Izinova® or Klean-Prep®) will be administered on Day 1
- Colonoscopy will be performed on Day 2
- Subjects will be contacted by phone on Day 4 ±1
- Subjects will come for a final follow-up visit on Day 32 (-5/+15 i.e. ranging from Day 27 to Day 47)

An overview of the study design is presented in Figure 1.

Figure 1 Study Design



V1=Visit 1, V2=Visit 2, V3=Visit 3, V4=Visit 4

3.2 Primary and Secondary Endpoints and Evaluations

3.2.1 Primary Efficacy Endpoints and Evaluations

Non-inferiority of Eziclen®/Izinova® versus Klean-Prep® in the cleansing of the colon:

The primary efficacy will be assessed by blinded overall assessment of preparation efficacy (Cleansing Score) as determined by the colonoscopist upon completion of the examination, based on a 4-point scale:

Score	Grade	Description
4	Excellent	No more than small bits of adherent faeces/fluid
3	Good	Small amounts of faeces or fluid not interfering with examination
2	Fair	Enough faeces or fluid to prevent a completely reliable examination
1	Poor	Large amounts of faecal residue, additional cleansing required

Only perfect preparations graded as excellent (4) or good (3), which allow full, reliable examination of the mucosa, will be considered as successful.

Primary efficacy will be assessed on the basis of preparation success or failure.

3.2.2 Secondary Endpoints and Evaluations

3.2.2.1 Efficacy Endpoints:

- Need to place a nasogastric tube to complete preparation
- Time to clear effluent (from first intake of preparation), as reported by the subject
- Need for rescue treatment (saline enema) because of inadequate preparation
- Cleansing Scores assessed by the 4-point scale (poor, fair, good, excellent)
- Overall and segmental Cleansing Scores assessed by Boston Bowel Preparation Scale (BBPS)
- Duration of intubation (from colonoscope introduction to caecal intubation)
- Duration of examination, measured by colonoscope withdrawal time from caecum
- Procedure documented as completed (procedures that reached the caecum)
- Treatment compliance: volumes of fluids measured by the caregiver and reported in the treatment questionnaire of subject's leaflet during treatment administration
- Treatment acceptability, assessed by Treatment Acceptability Questionnaire completed by caregiver or subject at the time of intake using a 5-point scale questionnaire to be filled in by the subject immediately after dosing

Very badly accepted/unacceptable	Subject showed great displeasure, compromising use of formulation
Badly but accepted	Subject showed displeasure with dosing but could be coaxed to take complete dose
Neither good nor bad	Subject showed no apparent displeasure and with little effort was coaxed to take complete dose
Well accepted	Subject appeared to enjoy the formulation and with little coaxing ingested complete dose
Very well accepted	Subject appeared eager and ingested complete dose without special coaxing

3.2.2.2 Safety and Tolerability Variables

- Collection of AEs (for up to 30 days following the day of colonoscopy)
- Tolerability assessed by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms
- Description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage
- Vital signs including body weight and physical examination
- Laboratory data: serum and urinary biochemistry:
  - Visit 1
  - Day 2 (colonoscopy)
  - Visit 4

3.3 Randomisation and Blinding

The sponsor's randomisation manager who is a statistician independent from the study will prepare two lists for this study.

- List A: a list of randomisation numbers will be produced in blocks, on a balanced ratio (one Eziclen®/Izinova®: one Klean-Prep®) and will be stratified by country
- List B: a list of treatment numbers will be produced in blocks, on a balanced ratio (one Eziclen®/Izinova®: one Klean-Prep®)

After eligibility is confirmed, at Visit 1 (Baseline), subjects will be assigned to a randomisation number and to the associated treatment arm, in sequential order within each centre and within each country.

This will be provided by the electronic case report form (eCRF) which will assign the subjects to the first not-used randomisation number and so in a treatment arm according to the predefined randomisation list.

The investigator will under no circumstances change the randomisation number and the treatment arm allocated to the subject.

Recruitment will stop once 250 subjects have been randomised. Randomised subjects who terminate their study participation for any reason before starting the treatment will retain their randomisation number (the randomisation number will not be reused). The next subject is given the next randomisation number.

Randomised subjects who leave the study early will not be replaced.

The sponsor's randomisation manager will keep the master lists (Lists A and B). A copy of the list of randomisation numbers (List A) will be confidentially supplied to the contract research organisation (CRO) in charge of the eCRF. Then, a copy of the list of treatment numbers (List B) will be confidentially supplied to the Chemistry, Manufacturing and Control Supply Chain (CMC-SC) (Beaufour Ipsen Industrie, Rue d'Ethe Virton, 28100 Dreux) and to the CRO in charge of the eCRF. The master lists and the copies supplied to the CRO in charge of eCRF and to the CMC -SC will be kept confidential in a secure location. Access to these lists must be restricted until authorisation is given to release them for final analysis.

3.4 Study Treatments and Dosage

Eziclen®/Izinova®:

The bowel cleansing preparation is a concentrate for oral solution packaged in two bottles, each of them contains: sodium sulphate anhydrous: 17.510 g, magnesium sulphate heptahydrate: 3.276 g, potassium sulphate: 3.130 g, sodium benzoate: CCI, sucralose: CCI and flavouring/taste masking agents (anhydrous citric acid, malic acid and a fruit cocktail flavour): CCI in aqueous liquid form.

Each treatment pack is composed of two bottles of 180 mL with about 176 mL of concentrate.

A more detailed description of administration procedures is given in Section 6.1.1.

Klean-prep®:

Klean-prep® is provided as powder for oral solution in sachets containing a whitish powder which, when dissolved in water, gives a clear, colourless solution for oral administration. Each sachet contains: macrogol 3350: 59.000 g, anhydrous sodium sulphate: 5.685 g, sodium bicarbonate: 1.685 g, sodium chloride: 1.465 g, potassium chloride: 0.7425 g. Klean-prep® should be stored at the recommended temperature (not above 25°C). A total of 69 g of the product (powder for oral solution) is included in one sachet. Each treatment pack is composed of 4 sachets.

A more detailed description of administration procedures is given in Section 6.1.2.

In this single-blinded study, to ensure an unbiased evaluation of the study preparations, the colonoscopist will not be allowed to perform any study drug related activities (randomisation, drug dispensing, return and accountability, acceptability, tolerability and review of subject's leaflet/questionnaires). Any failure to maintain blinding of the treatment for the colonoscopist will be documented as a protocol violation. Subjects and caregivers will be instructed not to discuss their study preparation with the colonoscopist or any staff member other than with the study nurse who will collect the questionnaires.

A rescue treatment (normal saline enema, 1000 mL) may be administered only if clear discharge has not been obtained 1 hour prior to procedure. This rescue medication will be given repeatedly until clear discharge is obtained. Sodium phosphate enemas are not to be used. The need for a rescue treatment will be recorded in the eCRF.

The investigational medicinal product (IMP) Eziclen®/Izinova® and Klean-PREP® will be packaged and released by the Beaufour Ipsen Industrie, CMC-SC and delivered to the investigational sites or deposited in an Interim Storage Facility. A sufficient quantity of Eziclen®/Izinova® and Klean-Prep® will be supplied as well as an acknowledgement of receipt form. The Sponsor's representative will receive a Certificate of Analysis for the IMP batches of the study, Material Safety Data Sheet for both active and comparative treatment, Packaging order and the Certificate of Compliance which reflects the product's release statement and will provide them to the sites according to local requirements.

The core label texts for all packaging units will be translated and/or adjusted, to be in compliance with applicable regulatory requirements, national laws in force and in accordance with the local languages. A non exhaustive description of the core text of the IMP labels is displayed below:

- Sponsor name,

- Study number,
- Pharmaceutical dosage form,
- Route of administration,
- Quantity of dose units,
- Batch number,
- Treatment number,
- Subject number (empty field to be completed by the pharmacist),
- Investigator name
- "Keep out of reach of children",
- "For clinical study use only",
- Name, address and telephone number of the sponsor, CRO or investigator (the main contact for information on the product, clinical study and emergency unblinding),
- Storage conditions,
- Expiry date.

The unblinded designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP carrying his/her number. The dispensing for each subject will be documented in the eCRF by unblinded pharmacist.

3.5 Study Duration

This study will consist of a 1-day enrolment (Day 1, baseline) and investigator-blind label dosing period, a 1-day colonoscopy (Day 2) and a 30-day follow-up period (Day 32 (-5/+15, i.e. Day 27 to Day 47). Subjects are expected to participate in this study for a minimum of 27 days and up to 47 days.

The subject's participation in the study will be considered to have ended at the time of the last visit (30 days after last IMP intake).

The study will be considered to have started when the first subject has been screened and provided signed informed consent. The Baseline visit (Visit 1) will be performed on the same day of treatment administration. Subjects meeting all eligibility criteria will be randomised to receive either Eziclen®/Izinova® or Klean-Prep® solution. After having received either Eziclen®/Izinova® or Klean-Prep® solution, subjects will undergo colonoscopy. Subjects will be contacted by phone on Day 4 and will come on Day 32 for a safety follow-up visit.

As the blood and urine sulfate assay are not standard tests, the samples are transported in batches to an overseas central laboratory and processed there. Results are transferred to the study database. The last sample is taken at the time of last subject last visit. The estimated duration for transfer of the sample to the central laboratory, processing and transfer of the results to the database is approximately 6 weeks. In order to ensure that the sulfate data are included in the CSR, the end of study is being redefined. The study will be considered to have ended after the last subject last external data from central laboratory has been transferred to the database.

The overall duration of the study will be approximately 32 months (30 months of recruitment + 1 month of follow-up + 6 weeks minimum for last data transfer).

3.6 Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, SAEs will be reviewed (see Section 8.1.4) as they are reported from the study centre to identify safety concerns. An Expert Committee will be appointed to review safety data. This Expert

Committee will be chaired by the principal investigator. Full details of the operating model for this safety data review will be provided in a charter to be produced.

The study may be terminated by the sponsor at any time.

A subject may discontinue participation in the study at any time for any reason (e.g. lack of efficacy, withdrawal of consent, AE). The investigator and/or sponsor can withdraw a subject from the study at any time for any reason (e.g. protocol violation or deviation as defined in Section 12.1.2, noncompliance with the protocol conditions or AE).

3.7 Investigational Medicinal Product Preparation Storage and Accountability

3.7.1 Investigational Medicinal Product Storage and Security

The unblinded approved representative (e.g. pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.

3.7.2 Investigational Medicinal Product Preparation

The unblinded approved representative (e.g. pharmacist), will ensure that all IMP and comparative treatment are reconstituted and dispensed by qualified staff members (Refer to 6.1 for details).

3.7.3 Investigational Medicinal Product Accountability and destruction

All IMP and any other study related material is to be accounted for on the IMP accountability log provided by the sponsor. It is essential that all used and unused supplies are retained for verification (by the sponsor or sponsor's representative). The pharmacist or nurse should ensure adequate records are maintained in the IMP accountability log.

All used and unused components of study preparation must be accounted for on the drug inventory log and will be returned to the sponsor at the completion or termination of the study, unless instructed otherwise by the sponsor.

3.8 Maintenance of Randomisation and Blinding

This study being investigator-blinded, the eCRF will provide two user profiles: one profile (e.g. pharmacist) which will be able to see the treatment arm and another one for the investigator for whom this information will be hidden. The tear-off of pack labels will indicate the treatment number to be entered in the eCRF, it will be similar for Eziclen®/Izinova® and Klean-Prep®. However, the appearance and contents of packs being different, to maintain the blinding for the investigator, the randomisation/dispensation of assigned treatment will be done by a pharmacist/nurse in charge of this activity. This person will be fully trained about the importance of his role in maintaining the blind for the investigator.

Two sets of individual sealed code break envelopes (refer to List B) will be prepared by the sponsor's randomisation manager to enable emergency code break procedures for individual subjects without compromising the blind of the study. One set will be provided to the investigational site and one set will be provided to the Global Patient Safety of the sponsor. The sending of code-break envelopes "investigator" will have to be coordinated with the sending of associated treatment kits.

Code break envelopes will only be opened in cases of medical emergency when treatment is dependent on knowledge of the IMP received.

In an emergency situation, which requires the identification of the study treatment group, the investigator may break the treatment code immediately, or as quickly as possible if he/she finds it is in the best interest of the trial subject.

Once it has been determined that knowledge of the treatment code is necessary, the investigator will ascertain the subject's identification number and treatment number and then break the blind for the subject concerned. The investigator will then sign date and provide reason for the code break on the Emergency Code break form and on the code break envelope.

At the earliest opportunity the investigator is requested to inform the monitor in charge of his/her centre that the blind has been broken for an emergency.

Monitors should routinely check the integrity of the envelopes that are stored at the study site. They must collect envelopes from the study site prior to study close out and ensure that they are all intact. If envelope(s) have been opened at the site or by the sponsor's representative, the monitor must ensure a written explanation is clearly documented (opener's name, dated signature and reason for opening) on the visit status page of the eCRF.

Confirmation of the integrity of all code break envelopes at study completion must be documented in the trial master file (TMF). All sets of the sealed individual subject envelopes must be kept in the TMF in the co-ordinating office at study completion for proof of integrity.

3.9 Source Data Recorded on the Case Report Form

Data will be collected in the eCRF in compliance with FDA 21 CFR Part 11. As required by GCP, the sponsor assigned monitor will verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the eCRF.

The source documents must, as a minimum, contain a statement that the subject is included in a clinical study, the date that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), IMP administration and any AEs and associated concomitant medication.

As required by ICH GCP Section 6.4.9, if some items are recorded directly on the eCRF and are considered as source data, the identification of these data must be documented and agreed between the investigator and the sponsor.

Definitions for source data and source documents are given below:

- **Source Data**: All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
- **Source Documents**: Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x rays, subject files and records kept at the pharmacy, at the laboratories and at medicotechnical departments involved in the clinical study).

The subject must have consented to their medical records being viewed by the sponsor's authorised personnel, and by local and possibly foreign, Competent Authorities (CA). This information is included in the informed consent.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subject MUST satisfy all of the following entry criteria before being allowed to participate in the study:

(1) Provision of signed ICF to participate in the study obtained from the adolescent's parent(s)/ legal representative and a signed assent form from the adolescent according to local law

(2) Male or female subjects between 12 to 17 years of age (inclusive)

(3) Body weight more than 40 kg

(4) Female of childbearing potential must have a negative pregnancy test

(5) If female, and of child-bearing potential, subject must use an acceptable form of birth control (hormonal birth control, intrauterine device (IUD), double-barrier method, or depot contraceptive)

(6) Routinely accepted indication for undergoing colonoscopy, including but not limited to polyposis coli diagnosis or surveillance, gastrointestinal bleeding, unexplained diarrhoea or constipation, surveillance of inflammatory bowel disease or confirmation of mucosal healing, abdominal pain, abnormal endosonography or manometry, anaemia of unknown aetiology, cancer surveillance

(7) In the investigator’s judgment, the parent(s)/legal representative are/is mentally competent to provide informed consent for the subject to participate in the study

(8) In the investigator’s judgement, subject is able and willing to follow study procedures including drug administration and response to questionnaires

4.2 Exclusion Criteria

If any of the following apply, the subject MUST NOT enter/continue in the study:

(1) Subject with known or suspected ileus, gastrointestinal obstruction, gastric retention (gastroparesis), rectal impaction, toxic colitis, severe ulcerative colitis or toxic megacolon, advanced carcinoma, swallowing disorders

(2) Subject with known or suspected inflammatory bowel disease (Crohn’s disease, ulcerative colitis) in moderate to severe active phase defined by PCDAI >30 (Crohn’s disease) or PUCAI >34 (ulcerative colitis)

(3) Subject with bowel perforation or increased risk of bowel perforation, including connective tissue disorders or recent bowel surgery

(4) Subject with previous significant gastrointestinal surgery (e.g. colostomy, colectomy, gastric bypass, stomach stapling)

(5) Subject with uncontrolled pre-existing electrolyte abnormalities, or with electrolyte abnormalities based on Visit 1 laboratory results such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalaemia, hypocalcaemia, uncorrected dehydration, or secondary to the use of medications such as diuretics or angiotensin converting enzyme (ACE) inhibitors judged clinically significant by the investigator

(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m2 as calculated by using the Schwartz bedside equation* [13]), liver (ascites, Child-Pugh C), cardiac insufficiency (including congestive heart failure all grades) or hyperuricemia

*The estimated GFR will be calculated in patients with elevated creatinine at baseline.

(7) Female subject who is pregnant or lactating
(8) Subject who has participated in another investigational drug treatment within the last 90 days before the first study visit
(9) Subject with phenylketonuria
(10) Subject with history of asthma or hypersensitivity to any ingredient of either drug product
(11) Subject for whom intake of substances likely to affect gastrointestinal motility or urinary flow rate is required
(12) Subject with requirement to take any other oral medication within 3 hours of starting the bowel preparation, as this may impact medication absorption
(13) Subject with tendency for nausea and/or vomiting
(14) Subject with impaired consciousness that predisposes them to pulmonary aspiration or who have known swallowing disorders
(15) Subject with history of major medical/psychiatric conditions that, in the judgment of the investigator, would compromise safety in the study
(16) Subject with mental or psychiatric condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude
(17) Subject with a condition that, in the opinion of the investigator, might increase the risk to the subject or decrease the chance of obtaining satisfactory data needed to achieve the objectives of the study
(18) Subject who has previous enrolment in this study or concomitant enrolment in other clinical studies

4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, pregnancy (see Section 8.1.5), or other reasons concerning the health or wellbeing of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the study as described in Sections 3.6, 5.2.4.2, 6.2 and 8.1.7.

Should a subject decide to withdraw from the study after administration of IMP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2.4.2) and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal from the study must be recorded on the eCRF. If a subject withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an AE or a clinically significant laboratory test abnormality, monitoring will continue until the event has resolved or stabilised, until the subject is referred to the care of a local health care professional, or until a determination of a cause unrelated to the IMP or study procedure is made. The specific AE or test result(s) must be recorded on the eCRF. All evaluations should be performed, according to the protocol, on the last day the subject receives IMP, or as soon as possible thereafter. If the final visit is conducted more than 47 days after the

dose of IMP, all safety evaluations will be performed. It is not planned to collect efficacy data after Visit 2.

5 STUDY PROCEDURES

5.1 Study Schedule

The schedule of procedures and assessments during the study is summarised in Table 4.

Table 4 Study Procedures and Assessments

Study Period	**Baseline/ Treatment**	**Colonoscopy**	**Phone contact**	**End of Study (or in case of Early Withdrawal*)**
Visit	**1**	**2**	**3**	**4**
Day	**Day 1**	**Day 2**	**Day 4**	**Day 32**
Window			±1	**-5/+15 i.e. Day 27 to Day 47**
Eligibility Criteria	X			
Demographic Data	X			
Blood Pregnancy Test [a]	X			
Informed Consent (parent(s) or legal representative)	X			
Assent (subject)	X			
Medical and Surgical History	X			
Indication(s) for Colonoscopy	X			
Prior and Concomitant Medication [b]	X	X		X
Prior and Concomitant Non-Drug Therapy [b]	X	X		X
AEs [c]	X[d]	X	X[e]	X
Physical Examination	X			X
Vital Signs (Temperature, blood pressure (BP) and heart rate (HR)	X	X		X
Body Weight and height[f]	X	X		X
Blood sample collection [g], [h]	X[i]	X[j]		X
Urine sample collection[k]	X	X		X
Blood and urine sulphates[l]	X	X[j]		X
RANDOMISATION [m]	**X**			
Study treatment dispensation (with explanation of treatment administration)	X			
Subject/caregiver leaflet dispensation by study nurse (with explanation of questionnaires including compliance measurement)	X			
Subject takes treatment preparation	X			
Completion of leaflet questionnaires by subject/ caregiver/ nurse				
• Treatment / Compliance	X			
• Treatment Acceptability	X			

Study Period	Baseline/ Treatment	Colonoscopy	Phone contact	End of Study (or in case of Early Withdrawal*)
• Symptom Scale (Tolerability)	X			
Collection of leaflet questionnaires by study nurse		X		
Drug accountability/ study administration compliance by unblinded site member		X		
Colonoscopy assessment [n]		X		
Subject status at the end of the visit	X	X	X	X

*Early withdrawal will be anytime from Visit 1 (Refer to Section 3.6)
[a] If applicable. Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.
[b] Prior and concomitant medication and non-drug therapy will from 7 days before baseline and for any action taken by the investigator
[c] AEs will be actively collected by the investigator and subjects will be instructed to contact the investigator if they experience any AEs
[d] At baseline, AEs will be collected from the date of informed consent and assent signature
[e] The investigator will contact the subject by phone on Day 4±1 to collect data on potential AEs
[f] Height will be measured at Baseline only
[g] Local laboratory (blood): biochemistry including: anion gap, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactic dehydrogenase (LDH), gamma-glutamyl transferase (GGT), total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, C reactive protein (CRP), uric acid, creatinine clearance (calculated GFR), osmolality
[h] Laboratory assessments performed within 10 days or less prior to inclusion may be used to determine eligibility upon investigator agreement.
[i] Additional local laboratory haematology: complete blood count (CBC), international normalised ratio (INR), (Section 8.2.1)
[j] Blood sampling during anaesthesia
[k] Local laboratory urine analysis (by dipstick), microscopic examination
[l] Collection of blood and urine sample for central laboratory sulphate dosage
[m] Randomisation if satisfactory biochemistry results
[n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, diagnosis/findings.

Table 5 Subject's Leaflet Collected Information

	During/after Dose 1 Day 1	During/after Dose 2 Day 1
Treatment/Compliance Questionnaire[a]	X	X
Treatment Acceptability Questionnaire	X	X
Symptom Scale (Tolerability)	X	X
Information about time to bowel movement and time to first clear watery stool.		X

a Treatment/Compliance questionnaire will collect information about: preparation of treatment, treatment intakes (recording of residual volumes, start/end times) for Eziclen®/Izinova® or Klean-Prep®.

The total volume of blood drawn for all evaluations throughout this study is approximately 16.5 mL for each subject.

The total amount of blood to be collected from all subjects is presented in Table 6.

Table 6 Blood Volume Calculation

Description	Number of Samples	Volume (mL)	Total Volume (mL)
Haematology	1	3 mL	3 mL
Biochemistry	3	2.5 mL	7.5 mL
Sulphates	3	2 mL	6 mL
Total Volume (mL)			16.5 mL

5.2 Study Visits

5.2.1 Prescreening Period

The prescreening period is defined as the period between the visit where the colonoscopy indication is posed and the date of Visit 1. During this period, and prior to the study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject and subject's parent (s) or legal representative. An ICF will be provided to each parent/legal representative, and an assent form will be provided to each subject during the pre-screening period, when the indication for colonoscopy is decided. The documents are to be dated and signed before any study screening procedures, according to local IRB/IEC requirements.

5.2.2 Baseline/Treatment visit (Visit 1)

Each subject's assent and subject's parent(s)/legal representative consent forms, signed and dated will be retained by the investigator. The subject will be hospitalised and will be allocated a subject number. All subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required. The baseline visit (Visit 1) will take place on the day of hospitalisation for bowel preparation administration, after retrieving the signed ICF and assent form.

Dietary recommendations for this study are as follows: subjects will come on the morning of Visit 1 under fasting conditions. Starting with breakfast, the subjects may only have clear liquids on the day prior to colonoscopy until completion of the colonoscopy the following day. Non-adherence to the dietary recommendations (nature and date/time) will be recorded in the patient leaflet.

The following baseline assessments will be performed by the investigator/study nurse:

- Eligibility check (inclusion/exclusion criteria)
- Demographic data (date of birth[1]/age, sex),
- Medical and surgical history, including ongoing medical history, as well as any significant conditions, including but not limited to major abdominal surgeries (excludes appendectomy), renal failure/dysfunction, liver failure/dysfunction, cardiac disorders inflammatory bowel disease, polyposis, diabetes, cancer (must indicate type of cancer), immune system disorders, electrolyte abnormalities
- Physical examination

1 depending on regulatory requirements, the date of birth may not be collected entirely, only the year will be collected

- Pubertal stage, if available (Tanner stage)
- Body weight and height
- Vital signs (temperature, supine and standing BP and HR)
- Blood sampling: Laboratory assessments performed within 10 days or less prior to inclusion may be used to determine eligibility upon investigator agreement.
  a) haematology: international normalised ratio (INR), CBC
  b) biochemistry including: anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, albumin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, total protein, CRP, uric acid, creatinine clearance (calculated GFR), osmolality
- Urine analysis by dipstick (pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity, urine microscopic examination
- Blood and urinary samples for sulphate measurement
- Blood pregnancy test, if female of child-bearing potential. Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.
- Indication(s) for colonoscopy to be collected
- Randomisation
- Drug accountability, study treatment dispensation by study nurse (with explanation of treatment administration)
- Subject/caregiver questionnaires dispensation by study nurse (with explanation of questionnaires including compliance measurement)
- Prior and concomitant medications including supplements, herbal medications and non-prescribed compounds
- Prior and concomitant non-drug therapies and surgical procedures
- Collection of AEs from the time of informed consent signature
- Subject status at the end of the visit

Records up to the time of premature termination should be completed. In the event that the subject was not receiving IMP, the primary reason will be recorded.

If any Visit 1 serum chemistry result is considered abnormal and clinically significant by the investigator result may be checked per investigator's decision. The abnormal significant result will be reported as an AE.

In case of non-inclusion of the subject, the primary reason will be recorded.

Following confirmation of eligibility for the study, subjects will be given a randomisation/treatment allocation number and allocated to one of the dosing groups specified in Section 6.1.

Caregivers and subjects will be provided with a subject leaflet containing instructions on how to administer the study preparation. Caregivers will be provided with a Treatment Acceptability Questionnaire (see Section 7.3.2.3) to report their child's experience with the study preparation, and a Symptom Scale to rate subject tolerability (see Section 8.6). Subjects/caregivers will complete these questionnaires during and after the treatment administration.

Subjects will be hospitalised for preparation. The treatment will be prepared by a nurse and administration will be monitored as described in Section 3.4. The nurse or caregiver will fill in

the questionnaires or ensure that the subject fills in, as appropriate. If a subject is unable to complete the preparation, a nasogastric tube will be placed.

The bowel cleansing preparation will be taken orally on the evening of the day before colonoscopy.

The following procedures will be performed during and after treatment administration:

- Treatment preparation taken by subject (nasogastric tube may be placed if needed for completion of preparation)
- Completion of subject leaflet (for Eziclen®/Izinova® or Klean-Prep® depending on allocated treatment arm) which contains:
    - Treatment administration, compliance, Treatment Acceptability Questionnaires and Symptom Scale by subject/caregiver
    - Information about bowel movement and stool
    - Time of first clear watery stool

5.2.3 Colonoscopy (Visit 2, Day 2)

Colonoscopy will be performed on the morning following completion of the preparation.

Subject's vital signs and weight will be measured. A blood sample will be collected during anaesthesia for sulphate assessment testing by central lab and for biochemistry testing by local lab. A urine sample will be collected prior to anaesthesia for sulphate measurement by central lab and another one for urinary analysis by local lab.

The colonoscopy will be performed by a physician according to the site's standard procedures. Cleanliness will be evaluated on a 4-point scale, as shown in Section 7.3.1 as well as using the BBPS (See Section 7.3.2.1). Additional data will be collected as outlined in Section 7.2.

The subject will be discharged from the hospital after the colonoscopy (unless there is a medical reason/condition for retaining the subject).

The following procedures will be performed on day of colonoscopy (Day 2):

- Review and recording of AEs
- Body weight
- Vital signs (temperature, supine BP and HR)
- Blood and urine sample for local lab
- Blood and urine sample for central lab sulphate testing
- Colonoscopy
- Colonoscopy-related assessments, including suspected diagnosis
- Histological examination of colonic biopsy (if needed)
- Drug accountability by unblinded site personal
- Reporting of study administration compliance data (based on subject's leaflet information) by unblinded site personal
- Subject status at the end of the visit

5.2.4 Procedures after Study Treatment

5.2.4.1 Phone Contact (Visit 3)

The investigator will contact the subject by phone on Day 4±1 to collect data on potential AEs.

5.2.4.2 End of Study Visit (Visit 4) or Early Withdrawal Visit

Subjects will return to the study centre 30 days (-5+/15 days) after colonoscopy. A physical examination will be performed, vital signs measured and the subject will be queried for occurrence of AEs and changes in concomitant medications. If any laboratory result is considered clinically significant by the investigator (and documented as an AE), a follow-up sample should be collected and sent for analysis. The subject will be followed-up until resolution of the AE.

For subjects who complete the study, or for those who withdraw prematurely from the study, final evaluations will be performed as soon as possible afterwards. Subjects with ongoing AEs or clinically significant laboratory test abnormalities (as determined by the investigator) will be monitored as described in Section 8.1.3 and Section 8.1.2.4, respectively.

The following procedures will be performed at the End of Study (Visit 4, Day 32 (-5/+15 days i.e. Day 27 to Day 47), or Early Withdrawal visit:

- Review of AEs
- New or changed concomitant medications
- Concomitant non-drug therapies
- Concomitant surgical procedures
- Physical examination
- Vital signs (temperature, BP and HR)
- Body weight
- Collection of blood and urine samples for blood sulphate measurement by central lab
- Collection of blood for biochemistry analysis and urine for local laboratory analysis
- Subject status at the end of the visit.

6 TREATMENT OF SUBJECTS

6.1 Study Drugs Administered

Following confirmation of eligibility for the study, subjects will be allocated to one of the following treatment groups:

- Eziclen®/Izinova® concentrate sulphate salt solution

or

- Klean-Prep®, powder for oral solution dosage

6.1.1 Eziclen®/Izinova®

The bowel cleansing preparation Eziclen®/Izinova® is a concentrate for oral solution packaged in two bottles, each of them contains: sodium sulphate anhydrous: 17.510 g, magnesium sulphate heptahydrate: 3.276 g, potassium sulphate : 3.130 g, sodium benzoate: CCI sucralose: CCI

Each treatment pack is composed of two bottles of 180 mL with about 176 mL of concentrate.

The bowel cleansing preparation Eziclen®/Izinova® will be given orally on the evening of the day before colonoscopy. The total dose administered is 3/4 of the adult dose (product dispensed).

Evening before the procedure (e.g.: 6:00 pm):

The two bottles of Eziclen®/Izinova® (180 mL X 2 concentrate sulphate salt solution) are to be diluted up to 1000 mL with water, using a 1000 mL graduated measuring glass. A total of 250 mL (1/4) of the preparation will be discarded. The remaining 750 mL of the preparation (3/4 adult dose) will be divided in two equal portions. The first portion of 375 mL will be drunk slowly in ½ to 1 hour, followed by an additional 750 mL of water over the next hour. The total ingested volume is 1125 mL.

Approximately 2 hours after the start of drinking the first portion (e.g., 8:00 pm):

The second 375 mL portion of the Eziclen®/Izinova® preparation will be drunk slowly in ½ to 1 hour followed by additional 750 mL of water over the next hour. The total ingested volume is 1125 mL.

The total volume of preparation drunk is 750 mL, with an additional 1500 mL of water, for a total of 2250 mL. If a subject experiences difficulty in drinking the bowel cleansing preparation, a nasogastric tube will be placed, the rate of administration should not exceed 30 mL/kg/hour.

6.1.2 Klean-Prep®

The comparator, Klean-Prep® is a powder for oral solution packaged in 4 sachets.

Each sachet of Klean-Prep® contains the following active ingredients: 59.000 g macrogol 3350, 5.685 g anhydrous sodium sulphate, 1.685 g sodium bicarbonate, 1.465 g sodium chloride and 0.7425 g potassium chloride.

Each treatment pack is composed of 4 sachets with a total of 69 g of the product (powder for oral solution) included in each sachet.

Klean-Prep® (powder for oral solution) will be given orally on the evening of the day before colonoscopy. The complete dose of the preparation will be administered on the day prior colonoscopy, in the evening.

Evening before the procedure (e.g.: 6:00 pm):

The 4 sachets are to be diluted. Each sachet is diluted in 1 litre of water. The dosage will be 70 mL/kg (which corresponds to the approved posology for that class of age and/or weight).

The volume to be taken will be calculated based on subject's weight and reported by study nurse or pharmacist on the subject's leaflet as a reference. The maximum volume administered will be 4000 mL.

The whole solution will be administered in two half doses (1 litre per hour), with a 1-hour pause between the two half doses.

Approximately 2 hours after the start of the drinking the first portion (e.g. 8:00 pm), the second portion of Klean-Prep® will be drunk.

If a subject experiences difficulty in drinking the bowel cleansing preparation a nasogastric tube will be placed, the rate of administration should not exceed 30 mL/kg/hour.

6.1.3 Rescue Treatment

A rescue treatment (normal saline enema, 1000 mL) may be administered only if clear discharge has not been obtained 1 hour prior to procedure. This rescue medication may be repeated until clear discharge is obtained. Sodium phosphate enemas are not to be used.

6.2 Prior and Concomitant Medication and Non-drug /Therapy

The use of concomitant medication will be recorded from 7 days prior to Visit 1 until completion of Visit 4 (Day 32(-5/+15), including sedation medications and intravenous fluids administered during colonoscopy.

No concomitant medication is forbidden. However, bowel cleansing will interfere with the absorption of medications. Concomitant oral medication administered within 1 to 3 hours of the start of the treatment and until the end of the cleansing process may be flushed from the gastrointestinal tract and the medication may not be absorbed properly. The therapeutic effect of regularly taken oral drugs with a narrow therapeutic index or short half-life (e.g. oral contraceptives, antiepileptic drugs, antidiabetics, antibiotics, levothyroxine, digoxin…) may be particularly affected.

Caution is advised in subjects with conditions, or who are using medications, inducing fluid or electrolyte disturbances, such as angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, lithium treatment, or other medications that might affect electrolyte levels. Caution is also advised when taking medicines known to prolong the QT interval.

6.3 Procedures for Monitoring Subject Compliance

In order to maintain the investigator-blind, administration compliance will be assessed by dedicated personnel based on measurement of unused preparation and fluid intake recorded by the subject/caregiver on the subject's leaflet. Data collected on the subject's leaflet will be reviewed outside of the colonoscopist's presence and will not be made available to the colonoscopist.

Data will be entered in the eCRF by unblinded personnel as single data entry (one person enters the data in the eCRF). Data verification will be performed by study monitor during on site visits.

7 ASSESSMENT OF EFFICACY

For the timing of assessments in this study, refer to the schedule in Table 4.

7.1 Primary Efficacy Endpoints and Evaluations

The primary efficacy endpoints are presented in Section 3.2.1.

Blinded overall assessment of preparation efficacy will be determined by the colonoscopist upon completion of the examination, based on the 4-point scale score presented in Section 7.3.1.

7.2 Secondary Efficacy Endpoints and Evaluations

Secondary efficacy endpoints and evaluations are summarised in Table 7.

Table 7 Secondary Endpoints and Evaluations

Endpoint	Timepoint	Evaluation
Colon cleansing	Visit 2 (Colonoscopy)	Cleansing Score assessed on 4 levels (4-point scale (see Section 7.3.1)
Overall and segmental cleansing assessed by BBPS	Visit 2 (Colonoscopy)	BBPS (see Section 7.3.2.1) Overall score [14]. Segmental score (left colon (LC), transverse colon (TC), right colon (RC)).
Time to clear effluent	Treatment	Time between first intake of prescription and first clear watery stool.
Complete procedure	Visit 2 (Colonoscopy)	Number (%) of complete procedures defined as procedures that reached the caecum
Duration of intubation	Visit 2 (Colonoscopy)	Time between the colonoscope introduction and the time to reach caecum
Duration of examination	Visit 2 (Colonoscopy)	Duration of colonoscope withdrawal from caecum
Need for rescue treatment because of inadequate preparation intake.	Visit 2 (before colonoscopy)	Number (%) of procedures that need a rescue treatment (saline enema)
Treatment acceptability	Treatment	Level of acceptability of treatment assessed using a 5-point Treatment Acceptability Questionnaire (see Section 7.3.2.3).
Need for nasogastric tube	Treatment	Number (%) of subjects who need a nasogastric tube to complete preparation
Treatment compliance	Treatment	Volume of fluid not taken (see Section 7.3.2.2)

7.3 Methods and Timing of Assessing, Recording, and Analysing Efficacy Data

Methods for assessing efficacy data are described below. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 14.1 and methods of analyses are discussed in Section 10.4.5.

7.3.1 Primary Efficacy Assessment

The primary efficacy variable is the proportion of subjects with successful overall preparation. The colonoscopist will be asked to score the quality of the bowel preparation using the following Cleansing Score (Table 8).

Table 8 Cleansing Score

Score	Grade	Description
1	Poor	Large amounts of faecal residue, additional cleansing required
2	Fair	Enough faeces or fluid to prevent a completely reliable examination
3	Good	Small amounts of faeces or fluid not interfering with examination
4	Excellent	No more than small bits of adherent faeces/fluid

Primary efficacy will be assessed on the basis of preparation success or failure.

Only perfect preparations graded as excellent (4) or good (3), which allow full, reliable examination of the mucosa, will be considered as successful.

7.3.2 Secondary Efficacy Assessment

7.3.2.1 Boston Bowel Preparation scale

The overall and segmental cleansing as assessed by BBPS [15] is presented in Table 9.

Table 9 Boston Bowel Preparation Scale

Score per segment	BBPS definition
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 and/or opaque liquid

This information (segmental cleansing) will be collected for the right, transverse and left colon. Scores per segment will be summed to provide overall cleansing score.

7.3.2.2 Treatment/Compliance

The treatment questionnaire will be completed by the caregiver or subject after the subject completes each dose of preparation. The subject/caregiver will provide information about treatment preparation, residual volumes of preparation (volumes not taken by the subject) and start and stop times of intake. For the Eziclen®/Izinova® treatment only, information about the residual volume of water will be reported.

7.3.2.3 Treatment Acceptability Questionnaire

The Treatment Acceptability Questionnaire will be completed by the caregiver or subject after the subject completes each dose of preparation. Caregivers will be asked to rate subject acceptability using the following categories (Table 10).

Table 10 Treatment Acceptability Questionnaire Categories

Very badly accepted/unacceptable	Subject showed great displeasure, compromising use of formulation
Badly but accepted	Subject showed displeasure with dosing but could be coaxed to take complete dose
Neither good nor bad	Subject showed no apparent displeasure and with little effort was coaxed to take complete dose
Well accepted	Subject appeared to enjoy the formulation and with little coaxing ingested complete dose
Very well accepted	Subject appeared eager and ingested complete dose without special coaxing

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

AEs will be monitored from the time that the subject and parent(s)/legal representative signed the informed consent and throughout the study (see Section 3.5 for a definition of the study duration) and will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

8.1.1 Definition of an Adverse Event

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run in or washout periods, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5).

8.1.2 Categorisation of Adverse Events

8.1.2.1 Intensity Classification

AEs will be classified as mild, moderate or severe according to the following criteria:

- **Mild**: symptoms do not alter the subject's normal functioning
- **Moderate**: symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the subject
- **Severe**: symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

8.1.2.2 Causality Classification

The relationship of an AE to IMP administration or comparator will be classified according to the following:

- **Related**: reports including good reasons and sufficient information (e.g. plausible time sequence, dose response relationship, pharmacology, positive dechallenge and/or rechallenge) to assume a causal relationship with IMP administration in the sense that it is plausible, conceivable or likely.
- **Not related**: reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with IMP administration.

8.1.2.3 Assessment of Expectedness

The expectedness of an AE shall be determined by the sponsor according to the IB for an unapproved IMP, or the SmPC or package insert (PI) for an authorised medicinal product that is being used according to the terms and conditions of the marketing authorisation. If the IMP or comparator has marketing authorisations in several countries with different SmPCs or PIs, one will be selected as the reference document for assessing expectedness.

The reference document for assessing expectedness of AEs/event in this study will be the current IB.

8.1.2.4 Laboratory Test Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- They require intervention or a diagnosis evaluation to assess the risk to the subject
- They are considered as clinically significant by the investigator.

8.1.2.5 Abnormal Physical Examination Findings

Clinically significant changes, in the judgement of the investigator, in physical examination findings (abnormalities) will be recorded as AEs.

8.1.2.6 Other Investigation Abnormal Findings

Abnormal test findings as judged by the investigator as clinically significant (e.g. electrocardiogram changes) that result in a change in IMP dosage or administration schedule, or in discontinuation of the IMP, or require intervention or diagnostic evaluation to assess the risk to the subject, should be recorded as AEs.

8.1.3 Recording and Follow-up of Adverse Events

At each visit, the subject should be asked a non-leading question such as: “How have you felt since starting bowel cleansing or the last visit/assessment?”

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP or comparative treatment will be recorded on the AE page(s) of the eCRF.

Each instance of adverse events that occur twice in the split dose regimen (e.g. nausea) will be recorded twice on the eCRF, if recovery is documented between both instances.

Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbation’s of pre-existing illnesses should be recorded.

Any AEs already recorded and designated as ‘continuing’ should be reviewed at each subsequent assessment.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE (i.e. IMP or other illness). The investigator is required to assess causality and record that assessment on the eCRF. Follow-up of the AE, after the date of IMP discontinuation, is required if the AE or its sequelae persist. Follow-up, that will include medical care, is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor’s clinical monitor or his/her designated representative.

8.1.4 Reporting of Serious Adverse Events

All SAEs (as defined below) regardless of treatment group or suspected relationship to IMP or comparator must be reported immediately (within 24 hours of the investigator’s knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

An SAE is any AE that:

(1) Results in death,

(2) Is life-threatening, that is any event that places the subject at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death,

(3) Results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further),

(4) Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions,

(5) Results in congenital anomaly/birth defect in the offspring of a subject who received the IMP,

(6) Is an important medical event that may not result in death, be life-threatening, or require hospitalisation but which, based upon appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

In addition to the above criteria, any additional AE that the sponsor or an investigator considers serious should be immediately reported to the sponsor and included in the corporate SAEs database system.

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the investigator or treating physician**. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for “seriousness” but is not an adverse experience and thus is not subject to immediate reporting to the sponsor.
- Preplanned or elective treatments/surgical procedures should be noted in the subject’s screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

Any SAE must be reported immediately (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the investigator at any time during the study period.

Any AE/SAE with a suspected causal relationship to IMP administration or comparator occurring at any other time after completion of the study must be promptly reported.

The following information is the minimum that must be provided to the sponsor pharmacovigilance contact within 24 hours for each SAE:

- Study number
- Centre number
- Subject number

- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the sponsor or representative as soon as it is available. The investigator should always provide an assessment of causality for each event reported to the sponsor. Upon receipt of the initial report, the sponsor will ask for the investigator's causality assessment if it was not provided with the initial report.

The investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

8.1.5 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected poststudy

Information regarding pregnancies must be collected on the AE page of the eCRF and reported to the sponsor as an SAE. The sponsor will request further information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

The investigator must instruct all female subjects to inform them immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the subject should continue until conclusion of the pregnancy, which may involve follow-up after the subject's participation in the study has ended.

8.1.6 Deaths

All AEs resulting in death during the study period must be reported as an SAE within 24 hours of the investigator's knowledge of the event.

The convention for recording death is as follows:

- AE term: lead cause of death ([e.g. multiple organ failure, pneumonia, myocardial infarction]),
- Outcome: fatal.

The **only exception** is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be "death" or "sudden death".

8.1.7 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IMP (see Section 4.3).

If the IMP or comparator is discontinued due to an SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.4).

In all cases, the investigator must ensure the subject receives appropriate medical follow-up (see Section 8.1.3).

8.1.8 Reporting to Competent Authorities/IECs/IRBs/Other investigators

The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the CA, IECs

and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements.

8.2 Clinical Laboratory Tests

Blood for clinical local laboratory tests will be collected at Visits 1, 2 and 4 for local laboratory.

At Visit 1: haematology and biochemistry.

At Visit 2 (during anaesthesia) and Visit 4 or early withdrawal visit: blood biochemistry.

Blood will be also collected at Visits 1, 2 and 4 for central laboratory serum sulphate testing.

Urinary sampling will be performed for local laboratory at Visits 1, 2 and 4 (or early withdrawal visit).

Additional urinary sample will be performed at Visits 1, 2 and 4 for sulphate dosage by central laboratory.

The investigator will review the safety laboratory test results, document the review and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 8.1.2.4 for abnormal laboratory tests that should be recorded as AEs).

All clinically relevant abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return to Baseline or to a level deemed acceptable by the investigator and the sponsor's clinical monitor (or his/her designated representative) or until the abnormality is explained by an appropriate diagnosis.

8.2.1 Haematology

Blood samples (3 mL) will be collected (in a potassium ethylene diamine tetra acetic acid (EDTA) tube) to assess the following parameters: CBC: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (nutrophils, lymphocytes, monocytes, eosinophils, basophils, and others), platelet count and international normalised ratio (INR).

8.2.2 Blood Biochemistry

Blood samples (2.5 mL) will be collected (in an activator gel tube) to assess the following parameters by local laboratory:

Anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, CRP, uric acid, INR, creatinine clearance (calculated GFR), osmolality

Blood samples (2 mL) will be collected for sulphate level dosage by central laboratory at Visits 1: Baseline/treatment Visit 2: Colonoscopy and Visit 4: end of study or early withdrawal study.

All the data will be reported in the eCRF by single data entry and monitored during on site visits.

8.2.3 Urinalysis

Fresh urine samples (at least 10 mL) will be collected to assess the following parameters: pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity by dipstick.

Microscopy will be performed, if indicated, but results will not be collected in the eCRF. Osmolality and ketones will be measured and the results will be reported in the eCRF. If in the opinion of the investigator there are any clinically significant abnormalities in microscopy, they will be recorded as an AE in the eCRF.

8.2.4 Pregnancy Test

A blood pregnancy test will be performed for all female subjects of childbearing potential at Visit 1 and if clinically indicated thereafter. Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.

Any adolescent female with childbearing potential becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 8.1.5.

8.3 Physical Examination

Physical examinations will be conducted at Visit 1 and End of Study (Visit 4) /Early Withdrawal.

Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

8.4 Vital Signs

Blood pressure and HR will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and HR will be recorded in standing position and after 5 minutes rest in supine position at visit 1, after 5 minutes rest in supine position at Visits 2 and 4. Absolute values and change from Baseline will be analysed.

Body temperature and weight will be recorded.

8.5 Histological examination of colonic biopsy

Should any macroscopic lesions suspected by the investigator to be induced by colonic lavage, the histological examination of the biopsies will be described and recorded as a TEAE.

8.6 Symptom Scale

This scale will be completed by the subject/caregiver at Visit 1, after treatment intake (Table 11). Subjects/caregivers will rate their overall experience of stomach cramping, stomach bloating and nausea on a 5-point scale, with 1=no symptoms, 2=mild, 3=bothersome, 4=distressing and 5=severely distressing symptoms. Symptoms rated from mild (2) to severely distressing (5) must be reported as an AE.

Table 11 Symptom Scale

	Overall experience on 5-point scale				
Symptom	1=no symptoms	2=mild	3=bothersome	4=distressing	5=severely distressing
Stomach cramping					
Stomach bloating					
Nausea					

9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics are not assessed in this study.

10 STATISTICS

10.1 Analyses Populations

The following population will be used during statistical analyses:

- **Screened population**: All subjects screened (i.e. who signed the informed consent).
- **Safety population**: All randomised subjects with at least a partial dose of study medication. Subjects will be assessed according to the treatment received.
- **Intention to treat (ITT) population**: All randomised subjects who received even a partial dose of study drug. Subjects will be assessed according to their randomised treatment, regardless of the treatment they receive.
- **Modified Intention to treat Analysis Set (mITT):** All randomised subjects who received even a partial dose of study treatment and produced a primary efficacy assessment.
- **Per protocol (PP) population**: All subjects in the ITT population, who have undergone the colonoscopy procedure and for whom no major protocol violations/deviations occurred.

10.1.1 Populations Analysed

The primary analysis based on the primary efficacy endpoint will be performed on the mITT population. In that analysis, subjects who do not undergo colonoscopy because of inadequate preparation or preparation-related AEs will be considered as failures. In addition, robustness of primary efficacy results will be assessed by repeating the primary analysis on the PP population.

The analyses of safety data will be performed based on the safety population.

10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses

Any major protocol deviation will be described in the Protocol Deviation Document (PDD) and its impact on inclusion in each analysis population (mITT/PP population) for any subject will be specified. The final list of protocol deviations impacting the mITT/PP population will be reviewed during the data review meeting held prior to database lock. The list will be updated to include any additional major protocol deviations impacting inclusion in the PP population.

10.2 Sample Size Determination

The primary aim of the study is to show that Eziclen®/Izinova® is not inferior to Klean-Prep® in the proportion of subjects with successful colon cleansing.

A non-inferiority margin of 15% has been selected for consistency with other studies in colon cleansing preparations.

Therefore assuming a success rate (excellent or good response) of 85% in both the Eziclen®/Izinova® and Klean-Prep® groups, a one-sided alpha of 0.025 and 90% power, 120 subjects are required per treatment group. Assuming a rate dropout/non-compliance to protocol of 4% based on previous studies and taking into account that subjects will be hospitalised for treatment administration, 125 subjects will be randomised in each treatment group, i.e. 250 subjects in total. Enrolment will be completed once 250 subjects have been randomised.

The primary endpoint of treatment success will be tested sequentially (hierarchical structure) with the first test being non-inferiority test based upon the treatment difference. A rejection of the null hypothesis will trigger superiority testing based upon the treatment difference.

The two hypothesis tests are hierarchically structured so that the second test (superiority) will only be considered if the first test (non-inferiority) is rejected. The superiority test is powered to detect an absolute difference of 18%. There is no alpha adjustment for the second test as a result of the hierarchical testing.

10.3 Significance Testing and Estimations

The primary endpoint of treatment success will be tested sequentially with the first test being non-inferiority test based upon the treatment difference.

A two-sided 95% CI for the difference of the two clinical success rates (Eziclen®/Izinova® minus Klean-Prep®) will be calculated. If and only if the lower limit of the CI is greater than the lower limit of equivalence region -15%, Eziclen®/Izinova® is proven to be not less effective than Klean-Prep®.

A rejection of the null hypothesis will trigger superiority testing based upon treatment difference. If the lower limit of the CI is greater than zero, Eziclen®/Izinova® is proven to be superior to Klean-Prep®.

10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry Department.

A statistical and analysis plan (SAP) describing the planned statistical analysis in detail with tables, figures and listings templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9.2 or higher).

10.4.1 Demographic and Other Baseline Characteristics

In order to ensure balance of treatment groups, descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, prior medications and prior non-drug therapy, etc.) will be presented by treatment group and overall for the ITT, mITT and PP populations if they differ by more than 10%.

10.4.2 Homogeneity of Treatment Groups

In order to assess the homogeneity of treatment groups at Baseline, descriptive statistics and other baseline characteristics will be tabulated for each treatment group along with 95% CI.

10.4.3 Subject Disposition and Withdrawals

The numbers and percentages of subjects enrolled and included in each of the ITT, mITT, PP and safety populations will be tabulated by country and centre. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were randomised, discontinued and completed at each of the study periods (e.g. active follow-up) will be tabulated by treatment group. Primary reasons for discontinuation of study treatment will be tabulated.

10.4.4 Pharmacokinetic Data

Not applicable.

10.4.5 Efficacy Evaluation

As indicated in Section 7.1, the primary efficacy variable is the proportion of subjects with successful overall preparation evaluated with the scale (from 1 to 4) of the Cleansing Score as assessed by the colonoscopist.

A successful preparation will be defined as excellent (4) or good (3) preparation.

A failure preparation will be defined as:

- Fair (2) or poor (1) according to bowel cleansing
- Any subject who did not have a colonoscopy based on the investigator's assessment of the cleansing (insufficient faecal output, unclear faecal discharge, etc.) or due to preparation related AEs.
- Any subject for whom cleaning was not adequate for evaluation.
- Any subject for whom rescue treatment (saline enema) was needed.

The proportion of subjects with successful colon cleansing (graded as excellent or good) will be summarised along with the 95% confidence interval (CI) using the standard Wald asymptotic CI. The primary efficacy endpoint will be analysed using a logistics regression model including country as stratified variable, the interaction between country and treatment will be also investigated. The formal hypothesis test result (p-value) for treatment difference will be presented together with a two-sided 95% CI for the difference in success rates. The non-inferiority will be demonstrated if the lower limit of the 95% CI of that difference is higher than -15%.

If the non-inferiority is demonstrated, the superiority will be analysed based upon treatment difference. If the lower limit of the CI is greater than zero, Eziclen®/Izinova® is proven to be superior to the Klean-Prep®.

Secondary efficacy endpoints are presented in Section 7.2.

Results will be tabulated by treatment group and overall using descriptive summary statistics (mean SD, median, interquartiles and ranges) or frequency count with two-sided 95% CI when appropriate.

Time to clear effluent data will be analysed by using survival methods. The results will be presented both in summary tables (number of events, censors, median and interquartile time to event with 95% CI…) and graphically in Kaplan-Meier plots by treatment group and overall. This will be detailed in the SAP.

Other secondary endpoints will be analysed using Cochran-Mantel-Hænszel (CMH) chi-square for count (percentage) adjusting for country effect and two-way analysis of variance (ANOVA) for continuous parameters including treatment, country and their interaction as covariates.

10.4.6 Adjustment for Country/Centre Effect

An adjustment for country effect will be planned for the analysis of primary efficacy by country as covariates.

Descriptive analysis by country will be carried out.

10.4.7 Safety Evaluation

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.

All AEs will be coded according to the MedDRA and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by subject, system organ class and preferred term.

Incidence of all reported TEAE and SAEs will be tabulated by treatment group and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of study medication.

A TEAE is defined as any AE that occurs during the active phase of the study if:

- It was not present prior to receiving the first dose of IMP, or
- It was present prior to receiving the first dose of IMP but the intensity increased during the active phase of the study.

All TEAEs will be flagged in the AEs listings.

Concomitant medication will be coded by using World Health Organisation (WHO) Drug Dictionary and will be summarised by treatment group and overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, SD and range as appropriate) by treatment group and overall will be presented for vital signs, BP, HR, clinical laboratory tests (blood and urine sample), physical examination, etc. at each assessment with change from Baseline. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. Shift tables will be presented of the number and percentage of subjects with low, normal or high values and normal or abnormal exams.

Frequency count with two-sided 95%CI when appropriate by treatment group and by overall will be presented for symptom questionnaire data (stomach cramping, stomach bloating and nausea) on a 5-point scale (see Table 11).

10.5 Subgroup Analyses

Descriptive statistics for primary endpoint may be provided per country.

10.6 Interim Analyses

No interim analysis will be performed.

An Expert Committee chaired by the principal investigator will review safety data. This review will be performed during blind data review meetings. Full details of the operating model for this safety data review will be provided in a charter to be produced.

11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

Authorised personnel from external CAs and sponsor authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the sponsor.

Auditors and inspectors must have direct access to study documents and site facilities as specified in Section 12.4 and to any other locations used for the purpose of the study in question (e.g. laboratories).

In the event of the site being notified directly of a regulatory inspection, the investigator must notify the sponsor's representative as soon as possible, to assist with preparations for the inspection.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

No changes from the final approved (signed) protocol will be initiated without the prior written approval or favourable opinion of a written amendment by the IEC/IRB, except when necessary to eliminate immediate safety concerns to the subjects or when the change involves only logistics or administration. The principal investigator and the sponsor will sign the protocol amendment.

12.1.2 Protocol Deviations, Violations and Exceptions

A protocol deviation is nonadherence to protocol specific study procedures or schedules that does not involve inclusion/exclusion criteria, primary objective evaluation criteria, and/or GCP guidelines. Deviations are considered minor and do not impact the study.

A protocol violation is any significant divergence from the protocol, i.e. nonadherence on the part of the subject, the investigator, or the sponsor to protocol specific inclusion/exclusion criteria, primary objective evaluation criteria and/or GCP guidelines. Protocol violations will be identified and recorded, by study centre personnel, on the eCRF.

As a matter of policy, the sponsor will not grant exceptions to protocol specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically and scientifically justified for a particular subject, prior approval from the sponsor and the responsible IRB/IEC, in accordance with the Standard Operating Procedure (SOP), is required before the subject will be allowed to enter the study. If investigative centre personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (a protocol violation), they must immediately inform the sponsor. Such subjects will be discontinued from the study, except in an exceptional instance following review and written approval by the sponsor and the responsible IRB/IEC, according to the applicable SOP.

12.2 Information to Study Personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by education, experience and training to perform their specific responsibilities. These study staff members must be listed on the study centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to all study staff, including the investigator and for ensuring their compliance with the protocol. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

12.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.

The sponsor is responsible for monitoring this data to verify that the rights and wellbeing of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.

Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage

areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.

The site must complete the eCRFs according to the sponsor monitoring manual, of the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor will use functions of the electronic data capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

Whenever a subject name is revealed on a document required by the sponsor (e.g. laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the initials visible and annotated with the subject number as identification.

12.4 Audit and Inspection

Authorised personnel from external CAs and the sponsor's authorised Quality Assurance personnel may carry out inspections and audits (see Section 11).

12.5 Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

13 ETHICS

13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1.6).

The FDA, 21 CFR Part 11, Electronic Records, Electronic Signatures and FDA, Guidance for Industry: Computerised Systems Used in Clinical Trials are a regulations which provides criteria for acceptance by the FDA, under certain circumstances, of electronic records, e-signatures and hand-written signatures executed to electronic records as equivalent to paper records and hand-written signatures on paper.

In addition, this study will adhere to all local regulatory requirements.

Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB for the study protocol/amendment(s), written ICF, assent form, any consent or assent form updates, subject emergency study contact cards, subject recruitment procedures (e.g. advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

After IEC/IRB approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically relevant aspects are concerned, the IEC/IRB must be informed and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

13.2 Informed Consent and Assent

Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IMP) from the subject's parent(s)/legal representative and an assent from the subject. Sufficient time will be allowed to discuss any questions raised by the subject and subject's parent(s)/legal representative.

The sponsor will provide a sample ICF and a sample assent. The both final versions controlled forms must be agreed to by the sponsor and the IEC/IRB and must contain all elements included in the sample forms, in language readily understood by the subject and parent(s)/legal representative. Each subject's original consent form and assent form, personally signed and dated by the subject and by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects and parent(s)/legal representative with a copy of their signed informed consent.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance, approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

As required by local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

13.4 Confidentiality Regarding Study Subjects

The investigator must assure that the privacy of the subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the sponsor, subjects will be identified not by their names, but by an identification code (e.g. initials and identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded on the CRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Recording of Study Data

In compliance with GCP, the medical records/medical notes, etc, should be clearly marked and permit easy identification of a subject's participation in the specified clinical study.

The investigator must record all data relating to protocol procedures, laboratory data, safety data and efficacy ratings on the eCRFs provided for the study. The investigator, by completing the signature log, may formally designate authority to complete eCRFs to appropriately qualified staff having certified user access to the eCRF. Subject/caregiver completed questionnaires will be printed.

The unblinded personnel must record all the data relating to IMP administration and subject's leaflet questionnaire.

The investigator must, as a minimum, provide an electronic signature (e-signature) to each case report book to attest to the accuracy and completeness of all the data. If any changes are made to the eCRF, after a form has been locked and electronically signed, the investigator will be required to perform an additional e-signature authorising agreement with any new information or changes to the eCRF.

All corrections on the eCRF will be automatically tracked and a reason for change is always required. In the eCRF, the audit trail function will allow the changes made to be viewed on each item entered.

14.2 Data Management

14.2.1 eCRF

Electronic Data Capture (EDC) will be utilised for collecting subject data. Each site is required to have a computer and internet connection available for site entry of clinical data. All entries in the eCRF will be done under the electronic signature of the person performing the action. This electronic signature consists of an individual and confidential username and password combination. It is declared to be the legally binding equivalent of the handwritten signature. Only sponsor authorised users will have access to the eCRF as appropriate to their study responsibilities. Users must have successfully undergone software application training prior to entering data into the eCRF.

Data management will be conducted by a CRO, directed by the sponsor's data management department. All data management procedures will be completed in accordance with the sponsor and the contracted CRO SOPs. Prior to data being received in-house at the assigned CRO, it will be monitored at the investigator site, (for further details please see Section 12.3 Monitoring Procedures). The eCRF and other data documentation removed from the investigator site(s) will be tracked by the CRO and the monitor.

The sponsor will ensure that an appropriate eCRF is developed to capture the data accurately, and suitable queries are raised to resolve any missing or inconsistent data. The investigator will receive their data, from the clinical study, in an electronic format (PDF files) which will be an exact copy of the eCRF, and will include the full audit trail, for archiving purposes and future reference.

Any queries generated during the data management process will also be tracked by the contracted data management CRO/will be raised within the EDC system. It is the central study monitor's responsibility to ensure that all queries are resolved by the relevant parties.

The sponsor will also ensure that SAE data collected in the eCRF are consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history and any medical terms (e.g. concomitant non-drug therapy, concomitant surgeries) will be performed by the CRO, directed by the sponsor's Biometry Group, and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA.

Each subject will be identified with a unique subject identification number. All study documents related to a subject will be identified with this subject number.

Subject's leaflet where all information with regards to treatment Administration questionnaire, Information about subject's bowel movement, Treatment Acceptability Questionnaire and Symptoms Scale completed by the subject/caregiver will be single-entered by unblinded personnel at the Investigational site in the eCRF put in place by the sponsor. The principal investigator will ensure that these data are complete and accurately represent the study subject information by electronically signing the e-CRF.

Subject's leaflet where all information with regards to treatment administration questionnaire will be used to enter some (summary) data in e-CRF by the authorised staff at the investigational site in the e-CRF.

14.2.2 Subject/Caregiver Leaflet/Questionnaires

After randomisation at Visit 1 the subject will be provided with:

- Either the Eziclen®/Izinova® leaflet
- Or the Klean-Prep® leaflet

The subject's leaflet will be printed on single copy paper and provided to the principal investigator/study nurse who will file it in the subject's medical/study file

The leaflet will contain:

- Section 1: for Dose 1
  a) The Treatment administration questionnaire for Dose 1
  b) The Treatment Acceptability Questionnaire after Dose 1
  c) Symptoms Scale

- Section 2: for Dose 2
  a) The Treatment administration questionnaire for Dose 2
  b) The Treatment Acceptability Questionnaire after Dose 2
  c) Symptoms Scale

- Section 3: after preparation intake but before colonoscopy

Questions to subject:

- Information about bowel movement (Time of first bowel movement, Time of first clear watery stool, Did you wake up during the night to have a bowel movement?).
- If it was necessary, would you agree to undergo preparation with this product again?

14.3 Record Archiving and Retention

During the prestudy and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the investigator have been discussed.

Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. The investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing out the site. The sponsor will inform the investigator, in writing, as to when these documents no longer need to be retained.

If the principal investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

15 FINANCING AND INSURANCE

15.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. Financial remuneration will cover the cost per included subject, based on the calculated costs of performing the study assessments in accordance with the protocol and the specified terms of payment will be described in the contract. The contract should describe whether costs for pharmacy, laboratory and other protocol required services are being paid directly or indirectly.

Financial Disclosure Statements will need to be completed, as requested by European and local regulations.

15.2 Insurance, Indemnity and Compensation

The sponsor will provide Product Liability insurance for all subjects included in the clinical study. Where required, a hospital specific indemnity agreement will be used.

16 REPORTING AND PUBLICATIONS OF RESULTS

16.1 Publication Policy

The sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the sponsor.

The results of this study may be published or communicated to scientific meetings by the investigators involved in the study. For multicentre studies, a plan for scientific publication and presentation of the results may be agreed and implemented by the study investigators or a Steering Committee. The sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the sponsor and authors (or authors' institution) after receipt of the proposed publication by the sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the sponsor's request for delay to the proposed publication should the sponsor reasonably deem premature to publish the results obtained at the then stage of the study.

16.2 Clinical Study Report

A final clinical study report (CSR) will be prepared according to the ICH guideline on structure and contents of CSRs. A final CSR will be prepared where any subject has signed informed consent, regardless of whether the study is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

17 REFERENCES

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18 LIST OF APPENDICES

Appendix 1 Protocol Amendment #1

STUDY NUMBER:	F-FR-58800-003
PROTOCOL TITLE:	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) ≥40 Kg.
OLD PROTOCOL VERSION NUMBER & DATE	Final Version: 12 August 2016
NEWAMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 2.0 (including Amendment 1): 13 January 2017

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		12 August 2016	13 January 2017
Page	**Section**	**WAS**	**IS**

1	Front page	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/ Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) ≥40 Kg.	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) >40 Kg.
1	Front page	Pharmacovigilance/Emergency Contact: PPD	Pharmacovigilance/Emergency Contact: PPD
5	Synopsis – Title of the study	**Title of study:** Efficacy, safety and tolerability of a bowel cleansing preparation (Eziclen/Izinova®) in paediatric subjects undergoing colonoscopy: a Phase III, multicentre, randomised, comparative versus Klean-Prep® (PEG-Electrolytes), administered on the day before colonoscopy, investigator-blinded, non-inferiority study in adolescents of 12 to 17 years of age (inclusive) ≥40 kg.	**Title of study:** Efficacy, safety and tolerability of a bowel cleansing preparation (Eziclen/Izinova®) in paediatric subjects undergoing colonoscopy: a Phase III, multicentre, randomised, comparative versus Klean-Prep® (PEG-Electrolytes), administered on the day before colonoscopy, investigator-blinded, non-inferiority study in adolescents of 12 to 17 years of age (inclusive) >40 kg.
5	Synopsis - Objectives	Primary objective: To demonstrate that Eziclen®/Izinova®, an osmotic sulphate-based laxative preparation given on the day before colonoscopy has non-inferior efficacy to Klean-Prep® (polyethylene glycol (PEG)-electrolytes) on colon cleansing in adolescents aged 12 to 17 years (inclusive) with a body weight ≥ 40 kg, scheduled to undergo a colonoscopy for a routinely accepted diagnostic indication	Primary objective: To demonstrate that Eziclen®/Izinova®, an osmotic sulphate-based laxative preparation given on the day before colonoscopy has non-inferior efficacy to Klean-Prep® (polyethylene glycol (PEG)-electrolytes) on colon cleansing in adolescents aged 12 to 17 years (inclusive) with a body weight >40 kg, scheduled to undergo a colonoscopy for a routinely accepted diagnostic indication

5	Synopsis - Methodology	In adolescents (male and female) ~~≥~~40 kg with routine indication for colonoscopy	In adolescents (male and female) > 40 kg with routine indication for colonoscopy
6	Synopsis - Inclusion criteria	(3) Body weight more than ~~or equal to~~ 40 kg	(3) Body weight more than 40 kg
6	Synopsis - Exclusion criteria	(1) Subject with known or suspected ileus, gastrointestinal obstruction, gastric retention (gastroparesis), rectal impaction, toxic colitis, severe ulcerative colitis or toxic megacolon, swallowing disorders	(1) Subject with known or suspected ileus, gastrointestinal obstruction, gastric retention (gastroparesis), rectal impaction, toxic colitis, severe ulcerative colitis or toxic megacolon, **advanced carcinoma,** swallowing disorders
6	Synopsis - Exclusion criteria	(5) Subject with uncontrolled pre-existing electrolyte abnormalities, or with electrolyte abnormalities based on Visit 1 laboratory results such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalaemia, hypocalcaemia, uncorrected dehydration, or secondary to the use of diuretics or angiotensin converting enzyme (ACE) inhibitors judged clinically significant by the investigator	(5) Subject with uncontrolled pre-existing electrolyte abnormalities, or with electrolyte abnormalities based on Visit 1 laboratory results such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalaemia, hypocalcaemia, uncorrected dehydration, or secondary to the use of **medications such as** diuretics or angiotensin converting enzyme (ACE) inhibitors judged clinically significant by the investigator
6	Synopsis - Exclusion criteria	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m2), liver (Child-Pugh C) ~~or~~ cardiac insufficiency (including congestive heart failure grade ~~III and IV~~)	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m2), liver (**ascites**, Child-Pugh C), cardiac insufficiency (including congestive heart failure **all** grade**s**) **or hyperuricemia**
7	Synopsis - Exclusion criteria	(10) Subject with history of hypersensitivity to any ingredient of either drug product	(10) Subject with history of **asthma or** hypersensitivity to any ingredient of either drug product

11-12	Synopsis - Schedule of procedure and assessments	Table "Schedule of procedure and assessments" ~~Urine~~ pregnancy Test *Footnote*: [a] If applicable	Table "Schedule of procedure and assessments" **Blood** pregnancy test *Footnote*: [a] If applicable. **Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.** (…) **[h] Laboratory assessments performed within 10 days or less prior to inclusion may be used to determine eligibility upon investigator review and agreement**
25	1.7 Population to Be Studied	The study will enrol adolescents aged 12 to 17 years (inclusive), with body weight ≥~~-~~40 kg, scheduled to undergo colonoscopy for a routine indication.	The study will enrol adolescents aged 12 to 17 years (inclusive), with body weight > 40 kg, scheduled to undergo colonoscopy for a routine indication.
26	2.1 Purpose of the Study	The purpose of the present study is to compare the efficacy, safety and tolerability of Eziclen®/Izinova® to those of Klean-Prep® in adolescents aged 12 to 17 years (inclusive) with body weight ≥40 kg scheduled to undergo a colonoscopy for a routinely accepted indication	The purpose of the present study is to compare the efficacy, safety and tolerability of Eziclen®/Izinova® to those of Klean-Prep® in adolescents aged 12 to 17 years (inclusive) with body weight > 40 kg scheduled to undergo a colonoscopy for a routinely accepted indication
26	2.2.1 Primary Objective	The primary objective of the study is to demonstrate that Eziclen®/Izinova®, an osmotic sulphate-based laxative preparation given on the day before colonoscopy has non-inferior efficacy to Klean-Prep® (PEG-electrolytes) on colon cleansing in adolescents aged 12 to 17 years (inclusive) with a body weight ≥40 kg, scheduled to undergo a colonoscopy for a routinely accepted diagnostic indication.	The primary objective of the study is to demonstrate that Eziclen®/Izinova®, an osmotic sulphate-based laxative preparation given on the day before colonoscopy has non-inferior efficacy to Klean-Prep® (PEG-electrolytes) on colon cleansing in adolescents aged 12 to 17 years (inclusive) with a body weight >40 kg, scheduled to undergo a colonoscopy for a routinely accepted diagnostic indication.
27	3.1 General Design and Study Schema	This is a multicentre, investigator-blinded, randomised phase III comparative study conducted in adolescents (male and female) ≥40 kg	This is a multicentre, investigator-blinded, randomised phase III comparative study conducted in adolescents (male and female) >40 kg

31	3.6 Stopping Rules and Discontinuation Criteria	There are no formal rules for early termination of this study. During the conduct of the study, SAEs will be reviewed (see Section 8.1.4) as they are reported from the study centre to identify safety concerns	There are no formal rules for early termination of this study. During the conduct of the study, SAEs will be reviewed (see Section 8.1.4) as they are reported from the study centre to identify safety concerns. **An Expert Committee will be appointed to review safety data. This Expert Committee will be chaired by the principal investigator. Full details of the operating model for this safety data review will be provided in a charter to be produced.**
34	4.1 Inclusion Criteria	3) Body weight more than ~~or equal to~~ 40 kg	3) Body weight more than 40 kg
34	4.2 Exclusion Criteria	(1) Subject with known or suspected ileus, gastrointestinal obstruction, gastric retention (gastroparesis), rectal impaction, toxic colitis, severe ulcerative colitis or toxic megacolon, swallowing disorders	(1) Subject with known or suspected ileus, gastrointestinal obstruction, gastric retention (gastroparesis), rectal impaction, toxic colitis, severe ulcerative colitis or toxic megacolon, **advanced carcinoma,** swallowing disorders
34	4.2 Exclusion criteria	(5) Subject with uncontrolled pre-existing electrolyte abnormalities, or with electrolyte abnormalities based on Visit 1 laboratory results such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalaemia, hypocalcaemia, uncorrected dehydration, or secondary to the use of diuretics or angiotensin converting enzyme (ACE) inhibitors judged clinically significant by the investigator	(5) Subject with uncontrolled pre-existing electrolyte abnormalities, or with electrolyte abnormalities based on Visit 1 laboratory results such as hypernatremia, hyponatremia, hyperphosphatemia, hypokalaemia, hypocalcaemia, uncorrected dehydration, or secondary to the use of **medications such as** diuretics or angiotensin converting enzyme (ACE) inhibitors judged clinically significant by the investigator
34	4.2. Exclusion criteria	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m2), liver (Child-Pugh C) ~~or~~ cardiac insufficiency (including congestive heart failure grade ~~III and IV~~)	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m2), liver (**ascites**, Child-Pugh C), cardiac insufficiency (including congestive heart failure **all** grade**s**) **or hyperuricemia**

35	4.2. Exclusion criteria	(10) Subject with history of hypersensitivity to any ingredient of either drug product	(10) Subject with history of **asthma or** hypersensitivity to any ingredient of either drug product
36	5.1. Study Schedule	Table4 ~~Urine~~ pregnancy Test	Table4 **Blood** pregnancy test
37	5.1. Study Schedule	Table 4 *Footnote*: [a] If applicable.	Table 4 *Footnote*: [a] If applicable. **Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.** (…) **[h] Laboratory assessments performed 10 days or less prior to inclusion may be used to determine eligibility upon investigator review and agreement**
38	5.2.2 Baseline/ Treatment visit (Visit 1)	Blood sampling: a) Haematology: CBC b) biochemistry including: anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, albumin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, total protein, CRP, uric acid, international normalised ratio (INR), creatinine clearance (calculated GFR), osmolality	Blood sampling: **Laboratory assessments performed within 10 days or less prior to inclusion may be used to determine eligibility upon investigator agreement** a) Haematology: CBC b) biochemistry including: anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, albumin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, total protein, CRP, uric acid, international normalised ratio (INR), creatinine clearance (calculated GFR), osmolality
39	5.2.2 Baseline/treatment visit	~~Urine~~ pregnancy test, if female of child-bearing potential	**Blood** pregnancy test, if female of child-bearing potential. **Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.**

43	6.2 Prior and Concomitant Medication and Non-drug /Therapy	… may be particularly affected.	… may be particularly affected. **Caution is advised in subjects with conditions, or who are using medications, inducing fluid or electrolyte disturbances, such as angiotensin converting enzyme inhibitors, calcium channel blockers, diuretics, lithium treatment, or other medications that might affect electrolyte levels. Caution is also advised when taking medicines known to prolong the QT interval.**
48	8.1.3 Recording and Follow-up of Adverse Events	Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.	Follow-up**, that will include medical care,** is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and the sponsor's clinical monitor or his/her designated representative.
52	8.2.4 Pregnancy test	A ~~urine~~ pregnancy test (…).	A **blood** pregnancy test (…). **Urine pregnancy test will be performed only when blood tests including pregnancy have been performed prior to Visit 1.**
57	10.6 Interim Analyses	No interim analysis will be performed.	No interim analysis will be performed. **An Expert Committee chaired by the principal investigator will review safety data. This review will be performed during data review meetings. Full details of the operating model for this safety data review will be provided in a charter to be produced.**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	F-FR-58800-003	
AMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 2.0 (including Amendment 1): 13 January 2017	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	Request of ANSM on Inclusion/Exclusion criteria, addition of information regarding safety data review.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*

	LOCAL CONSENT FORM UPDATE	Yes ☒ No ☐ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	STATISTICAL & ANALYSIS PLAN (SAP) UPDATE	Yes ☐ No ☒ *(tick one)*

Appendix 2 Protocol Amendment #2

STUDY NUMBER:	F-FR-58800-003
PROTOCOL TITLE:	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) >40 Kg.
OLD PROTOCOL VERSION NUMBER & DATE	Final Version 2.0 (including Amendment 1): 13 January 2017
NEWAMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 3.0 (including Amendment 2): 23 March 2017

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		13 January 2017	23 March 2017
Page	**Section**	**WAS**	**IS**

6	Synopsis	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m2), liver (ascites, Child- Pugh C), cardiac insufficiency (including congestive heart failure all grades) or hyperuricemia	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (**e**GFR) less than 30 mL/min/1.73 m2 **as calculated by using the Schwartz bedside equation* [Schwartz et al, 2009]**),** liver (ascites, Child-Pugh C), cardiac insufficiency (including congestive heart failure all grades) or hyperuricemia ***The estimated GFR will be calculated in patients with elevated creatinine at baseline.** **** Schwartz GJ and Work DF. Measurement and Estimation of GFR in Children and Adolescents. Clin J Am Soc Nephrol. 2009; 4: 1832–1843**
34	4.2 Exclusion criteria	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (GFR) less than 30 mL/min/1.73 m2), liver (ascites, Child-Pugh C), cardiac insufficiency (including congestive heart failure all grades) or hyperuricemia	(6) Subject with a prior history or current condition of severe renal (estimated glomerular filtration rate (**e**GFR) less than 30 mL/min/1.73 m2 **as calculated by using the Schwartz bedside equation* [13]**, liver (ascites, Child-Pugh C), cardiac insufficiency (including congestive heart failure all grades) or hyperuricemia ***The estimated GFR will be calculated in patients with elevated creatinine at baseline.**
69	17 References		**(13) Schwartz GJ and Work DF. Measurement and Estimation of GFR in Children and Adolescents. Clin J Am Soc Nephrol. 2009; 4: 1832–1843**

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	F-FR-58800-003	
AMENDED PROTOCOL VERSION NUMBER & DATE	Amendment 2 Final Version 3.0: 23 March 2017	
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒	
REASON(S) FOR CHANGES	Request of BfArM on Exclusion criteria, adding details of the method to calculate eGFR	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☐ No ☒ *(tick one)*

Appendix 3 Protocol Amendment #3

STUDY NUMBER:	F-FR-58800-003
PROTOCOL TITLE:	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) >40 Kg.
OLD AMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 3.0 (including Amendment 2): 23 March 2017
NEW AMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 4.0 (including Amendment 3): 17 July 2017

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		**23 MARCH 2017**	**17 JULY 2017**
Page	**Section**	**WAS**	**IS**
5	Planned study period	From ~~January~~ 2017 to ~~January~~ 2018	From **Q4** 2017 to **Q4** 2018

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	F-FR-58800-003		
AMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 4.0 (including Amendment 3): 17 July 2017		
SUBSTANTIAL ☐	**NON-SUBSTANTIAL** ☒		
REASON(S) FOR CHANGES	To update the study timelines		
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*	
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*	
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*	
	STATISTICAL & ANALYSIS PLAN (SAP) UPDATE	Yes ☐ No ☒ *(tick one)*	

Appendix 4 Protocol Amendment #4

STUDY NUMBER:	F-FR-58800-003
PROTOCOL TITLE:	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) >40 Kg.
OLD PROTOCOL VERSION NUMBER & DATE	Final Version 4.0 (including Amendment #3): 17 July 2017
NEWAMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 5.0 (including Amendment #4): 16 March 2018

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		17 July 2017	16 March 2018
Page	**Section**	**WAS**	**IS**
1	Cover	PPD	PPD
1	Cover	PPD	PPD
2	Signature page	Sponsor's Representative Signature: PPD 65 quai Georges Gorse 92100 Boulogne-Billancourt, France	Sponsor's Representative Signature: PPD 65 quai Georges Gorse 92100 Boulogne-Billancourt, France

		PPD	
9	Synopsis-Criteria for Evaluation	Safety and tolerability • Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms ~~• Description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage~~	Safety and tolerability • Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) - **Diagnosis or diagnostic findings made at colonoscopy will be reported as such and will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied. In this situation only, description of the colonoscopy findings and histological examination results will be reported as AEs.** • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms
12	Synopsis-Study procedure and Assessments	Indication for Colonoscopy Colonoscopy ~~efficacy~~ assessment [n] [n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time	Indication**(s)** for Colonoscopy Colonoscopy assessment [n] [n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, **diagnosis/findings (except if AE)**
29	3.2.2.2. Safety and Tolerability Variables	• Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach	• Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) - **Diagnosis or diagnostic findings made at colonoscopy will be reported as such and will not be reported as AEs unless the investigator**

		cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms • ~~Description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage~~	**observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied. In this situation only, description of the colonoscopy findings and histological examination results will be reported as AEs.** • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms
37	5.1. Study Schedule	Indication for Colonoscopy Colonoscopy ~~efficacy~~ assessment [n]	Indication**(s)** for Colonoscopy Colonoscopy assessment [n] [n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, **diagnosis/findings (except if AE, see Section 3.2.2.2.)**
40	5.2.2. Baseline/Treatment visit (Visit 1)	Indication for colonoscopy to be collected	Indication **(s)** for colonoscopy to be collected.
41	5.2.3. Colonoscopy (Visit 2, Day 2)	The following procedures will be performed on day of colonoscopy (Day 2): • … • Colonoscopy • Colonoscopy-related assessments • Histological examination of colonic biopsy (if needed)	The following procedures will be performed on day of colonoscopy (Day 2): • … • Colonoscopy • Colonoscopy-related assessments**, including suspected diagnosis** • Histological examination of colonic biopsy (if needed) • **Diagnosis or diagnostic findings made at colonoscopy will be reported as such and will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will**

			be biopsied. In this situation only, description of the colonoscopy findings and histological examination results will be reported as AEs.
48	8.1.1 Definition of an adverse event	This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5).	This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5). **Because colonoscopy is performed as a diagnostic procedure in this study, this definition specifically excludes diagnosis or diagnostic findings made during colonoscopy, such as ulcerative colitis, Crohn's disease or inflammatory bowel disease. These will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied. In this situation only, description of the colonoscopy findings and histological examination results will be reported as AEs.**
54	8.5	8.5 Histological examination of colonic biopsy Should any macroscopic lesions suspected by the investigator to be induced by colonic lavage, the histological examination of the biopsies will be described and recorded as a TEAE.	8.5 Diagnosis made at colonoscopy **Diagnosis or diagnostic findings made at colonoscopy will be reported as such and will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied.** **8.6** Histological examination of colonic biopsy Should any macroscopic lesions suspected by the investigator to be induced by colonic lavage, the histological examination of the biopsies will be described and recorded as a TEAE.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	F-FR-58800-003	
AMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 5.0 (including Amendment #4): 16 March 2018	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	Collect diagnosis/findings from colonoscopy Clarify to investigators that diagnoses made at colonoscopy are not to be reported as AEs.	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☒ No ☐ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*

Appendix 5 Protocol Amendment #5

STUDY NUMBER:	F-FR-58800-003
PROTOCOL TITLE:	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) >40 Kg.
OLD PROTOCOL VERSION NUMBER & DATE	Final Version 5.0 (including Amendment #4): 16 March 2018
NEWAMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 6.0 (including Amendment #5): 26 July 2018

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		16 March 2018	26 July 2018
Page	**Section**	**WAS**	**IS**

9	Synopsis-Criteria for Evaluation	Safety and tolerability • Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) ~~– Diagnosis or diagnostic findings made at colonoscopy will be reported as such and will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied. In this situation only, description of the colonoscopy findings and histological examination results will be reported as AEs.~~ • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms	Safety and tolerability • Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms • **Description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage**

12	Synopsis – Study procedures and assessments	[g] Local laboratory (blood): biochemistry including: anion gap, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactic dehydrogenase (LDH), gamma-glutamyl transferase (GGT), total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, C reactive protein (CRP), uric acid, international normalised ratio (INR), creatinine clearance (calculated GFR), osmolality … [i] Additional local laboratory haematology: complete blood count (CBC). … [n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, diagnosis/findings ~~(except if AE)~~	[g] Local laboratory (blood): biochemistry including: anion gap, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactic dehydrogenase (LDH), gamma-glutamyl transferase (GGT), total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, C reactive protein (CRP), uric acid, creatinine clearance (calculated GFR), osmolality … [i] Additional local laboratory haematology: complete blood count (CBC**), international normalised ratio (INR).** … [n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, diagnosis/findings
29	3.2.2.2. Safety and Tolerability Variables	Safety and tolerability • Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) ~~- Diagnosis or diagnostic findings made at colonoscopy will be reported as such and will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied. In this situation only, description of the colonoscopy findings and histological~~	Safety and tolerability • Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy) • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms • **Description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage**

		~~examination results will be reported as AEs.~~ • Tolerability by a Symptom Scale after each dose of treatment. Subjects will rate their preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptoms to 5= severely distressing symptoms	
38	5.1. Study Schedule	[g] Local laboratory (blood): biochemistry including: anion gap, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactic dehydrogenase (LDH), gamma-glutamyl transferase (GGT), total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, C reactive protein (CRP), uric acid, ~~international normalised ratio (INR)~~, creatinine clearance (calculated GFR), osmolality … [i] Additional local laboratory haematology: complete blood count (CBC**)** (Section 8.2.1) [n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, diagnosis/findings ~~(except if AE, see Section 3.2.2.2.)~~	[g] Local laboratory (blood): biochemistry including: anion gap, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactic dehydrogenase (LDH), gamma-glutamyl transferase (GGT), total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, C reactive protein (CRP), uric acid, creatinine clearance (calculated GFR), osmolality … [i] Additional local laboratory haematology: complete blood count (CBC**), international normalised ratio (INR)** (Section 8.2.1) [n] Colonoscopy assessment: Rescue treatment, cleansing Score, BBPS, start time of colonoscopy, time of caecal intubation, caecum reached, withdrawal time, diagnosis/findings.
40	5.2.2 Baseline/ Treatment visit (Visit 1)	• Blood sampling: Laboratory assessments performed within 10 days or less prior to inclusion may be used to determine eligibility upon investigator agreement. a) haematology: CBC b) biochemistry including: anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, albumin, creatinine, urea, serum electrolytes (sodium, potassium, chloride,	• Blood sampling: Laboratory assessments performed within 10 days or less prior to inclusion may be used to determine eligibility upon investigator agreement. c) haematology: **international normalised ratio (INR)**, CBC d) biochemistry including: anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, albumin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium,

		calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, total protein, CRP, uric acid, ~~international normalised ratio (INR),~~ creatinine clearance (calculated GFR), osmolality	magnesium, phosphorus, bicarbonate), alkaline phosphatase, total protein, CRP, uric acid, creatinine clearance (calculated GFR), osmolality
41	5.2.3. Colonoscopy (Visit 2, Day 2)	The following procedures will be performed on day of colonoscopy (Day 2): • … • Colonoscopy • Colonoscopy-related assessments, including suspected diagnosis • Histological examination of colonic biopsy (if needed) ~~• Diagnosis or diagnostic findings made at colonoscopy will be reported as such and will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied. In this situation only, description of the colonoscopy findings and histological examination results will be reported as AEs.~~	The following procedures will be performed on day of colonoscopy (Day 2): • … • Colonoscopy • Colonoscopy-related assessments**,** including suspected diagnosis • Histological examination of colonic biopsy (if needed)

48	8.1.1 Definition of an adverse event	This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5). ~~Because colonoscopy is performed as a diagnostic procedure in this study, this definition specifically excludes diagnosis or diagnostic findings made during colonoscopy, such as ulcerative colitis, Crohn's disease or inflammatory bowel disease. These will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied. In this situation only, description of the colonoscopy findings and histological examination results will be reported as AEs.~~	This definition includes events occurring from the time of the subject giving informed consent until the end of the study (as defined in Section 3.5).
52	8.2.1 Haematology	Blood samples (3 mL) will be collected (in a potassium ethylene diamine tetra acetic acid (EDTA) tube) to assess the following parameters: CBC: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others) ~~and~~ platelet count.	Blood samples (3 mL) will be collected (in a potassium ethylene diamine tetra acetic acid (EDTA) tube) to assess the following parameters: CBC: red blood cell (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils, and others)**,** platelet count **and international normalised ratio (INR).**
52	8.2.2 Blood Biochemistry	Anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, CRP, uric acid, ~~INR,~~ creatinine clearance (calculated GFR), osmolality	Anion gap, ALT, AST, CPK, LDH, GGT, total and conjugated bilirubin, creatinine, urea, serum electrolytes (sodium, potassium, chloride, calcium, magnesium, phosphorus, bicarbonate), alkaline phosphatase, albumin, total protein, CRP, uric acid, creatinine clearance (calculated GFR), osmolality
53	8.5	~~8.5 Diagnosis made at colonoscopy Diagnosis or diagnostic findings made at colonoscopy will be~~	

		~~reported as such and will not be reported as AEs unless the investigator observes mucosal lesions that he/she suspects to be related or possibly related to the colonic lavage. Such lesions will be biopsied.~~	

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	F-FR-58800-003		
AMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 6.0 (including Amendment #5): 26 July 2018		
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐		
REASON(S) FOR CHANGES	German competent authorities refused the Version 5.0		
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*	
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*	
	DATABASE UPDATE	Yes ☒ No ☐ *(tick one)*	
	REPORTING & ANALYSIS PLAN (RAP) UPDATE	Yes ☒ No ☐ *(tick one)*	

Appendix 6 Protocol Amendment #6

STUDY NUMBER:	F-FR-58800-003
PROTOCOL TITLE:	Efficacy, Safety and Tolerability of a Bowel Cleansing Preparation (Eziclen®/Izinova®) in Paediatric Subjects Undergoing Colonoscopy: a Phase III, Multicentre, Randomised, Comparative Study Versus Klean-Prep® (PEG-Electrolytes), Administered on the Day Before Colonoscopy, Investigator-Blinded, Non-Inferiority in Adolescents of 12 to 17 Years of Age (Inclusive) >40 Kg.
OLD PROTOCOL VERSION NUMBER & DATE	Final Version 6.0 (including Amendment #5): 26 July 2018
NEWAMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 7.0 (including Amendment #6): 02 March 2020

THE FOLLOWING AMENDMENT(S) IS/ARE PROPOSED:

Version Date		26 July 2018	02 March 2020
Page	**Section**	**WAS**	**IS**
5	Synopsis – Planned study period	From Q4 2017 to ~~Q4 2018~~	From Q4 2017 to **Q2 2020**
32	3.4	[…] The unblinded ~~investigator, or~~ designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP carrying his/her number. The dispensing for each subject will be documented in the eCRF by unblinded pharmacist.	[…] The unblinded designee, will only dispense IMPs to subjects included in this study. Each subject will only be given the IMP carrying his/her number. The dispensing for each subject will be documented in the eCRF by unblinded pharmacist.
32	3.5	[…]	[…] **As the blood and urine sulfate assay are not standard tests, the samples are transported in batches to an overseas central laboratory and processed there. Results are transferred to the study database. The last sample is taken at the time of last subject last visit. The estimated duration for transfer of the sample to the central laboratory, processing and transfer of the results to the**

		The overall duration of the study will be approximately ~~*13*~~ months (~~*12*~~ months of recruitment + 1 month of follow-up). […] The study will be considered to have ended after the last subject ~~has completed the last follow-up period in the study~~.	**database is approximately 6 weeks. In order to ensure that the sulfate data are included in the CSR, the end of study is being redefined.** The study will be considered to have ended after the last subject **last external data from central laboratory has been transferred to the database.** The overall duration of the study will be approximately ***32*** months **(*30* months of recruitment + 1 month of follow-up + *6 weeks minimum for last data transfer*).**
33	3.7.1	The unblinded ~~investigator, or an~~ approved representative (e.g. pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.	The unblinded approved representative (e.g. pharmacist), will ensure that all IMP and any other study related material is stored in a secured area, under recommended temperature monitored storage conditions, in accordance with applicable regulatory requirements.
33	3.7.2	The unblinded ~~investigator, or an~~ approved representative (e.g. pharmacist), will ensure that all IMP and comparative treatment are reconstituted and dispensed by qualified staff members (Refer to 6.1 for details).	The unblinded approved representative (e.g. pharmacist), will ensure that all IMP and comparative treatment are reconstituted and dispensed by qualified staff members (Refer to 6.1 for details).
34	3.8	[…] At the earliest opportunity the investigator is requested to inform the ~~blinded~~ monitor in charge of his/her centre that the blind has been broken for an emergency.	[…] At the earliest opportunity the investigator is requested to inform the monitor in charge of his/her centre that the blind has been broken for an emergency.
56	10.1.2	Any major protocol deviation will be described in the Protocol Deviation Document (PDD) and its impact on inclusion in each analysis population (mITT/PP population) for any subject will be specified. The final list of	Any major protocol deviation will be described in the Protocol Deviation Document (PDD) and its impact on inclusion in each analysis population (mITT/PP population) for any subject will be specified. The final list of protocol deviations

		protocol deviations impacting the mITT/PP population will be reviewed during the ~~blind~~ data review meeting held prior to database lock~~, before any unblinding of treatment groups~~. The list will be updated to include any additional major protocol deviations impacting inclusion in the PP population.	impacting the mITT/PP population will be reviewed during the data review meeting held prior to database lock. The list will be updated to include any additional major protocol deviations impacting inclusion in the PP population.
59	10.6	[…] An Expert Committee chaired by the principal investigator will review safety data. This review will be performed during data review meetings. Full details of the operating model for this safety data review will be provided in a charter to be produced.	[…] An Expert Committee chaired by the principal investigator will review safety data. This review will be performed during **blind** data review meetings. Full details of the operating model for this safety data review will be provided in a charter to be produced.

SUMMARY & OUTCOME OF CHANGES:

STUDY NUMBER	F-FR-58800-003	
AMENDED PROTOCOL VERSION NUMBER & DATE	Final Version 7.0 (including Amendment #6): 02 March 2020	
SUBSTANTIAL ☒	**NON-SUBSTANTIAL** ☐	
REASON(S) FOR CHANGES	- Modification of the end of study definition - Correction of minor inconsistencies	
OTHER ACTION REQUIRED?	CRF UPDATE	Yes ☐ No ☒ *(tick one)*
	LOCAL CONSENT FORM UPDATE	Yes ☐ No ☒ *(tick one)*
	DATABASE UPDATE	Yes ☐ No ☒ *(tick one)*
	STATISTICAL & ANALYSIS PLAN (SAP) UPDATE	Yes ☐ No ☒ *(tick one)*