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STATISTICAL ANALYSIS PLAN

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.

PROTOCOL VERSION AND DATE:
FINAL VERSION 7.0 – 02 MARCH 2020

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Final version 4.0	25 August 2020

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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.
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SAP DATE:	25 August 2020

Further to your review and agreement to the Statistical Analysis Plan version indicated above, please sign to indicate approval for your area of responsibility:

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IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical Analysis Plan version became the Final Statistical Analysis Plan

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	
1		11JUN2018 (v1.0)	18JUN2018 (v2.0)	Protocol version 5.0 (dated 18JAN2018) was indicated in SAP version 1.0, but this protocol was in fact not approved, so Protocol version 4.0 (dated 17JUL2017) was corrected in SAP version 2.0.
1		18JUN2018 (v2.0)	26FEB2020 (v3.0)	Following to protocol amendment version 5, protocol version 6.0 is then applicable.
14 21	1.4.2.1 3.1.2	18JUN2018 (v2.0)	26FEB2020 (v3.0)	The endpoint "duration of intubation" has been renamed to "time to caecal intubation", and the endpoint "time between the last intake of fluids and the start of colonoscopy procedure" has been added.
16 22	1.4.2.2 3.1.3	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Following to protocol amendment, safety assessments have been reviewed: - AE collection has been specified, i.e. "at Visit 4 Day 32 -5/+15". - Sentence about diagnosis and diagnostic findings has been removed, and description of mucosal lesions has been added. - And, the international normalised ratio (INR) is not considered as a biochemistry parameter anymore but as a haematology one.
22	3.1.5	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Since the secondary endpoints are not supposed to be tested for superiority according to the protocol, the corresponding sentence has been reviewed to specify that they will be tested for descriptive purpose only.
23	3.2.1	18JUN2018 (v2.0)	26FEB2020 (v3.0)	The secondary analyses will also be repeated on the PP population, and the other efficacy analyses will be repeated on the mITT population, if they differ from more than 10% from the ITT population; since this is important to check the robustness of the results if the populations differ too much.

23	3.2.1.1	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Primary analysis has been updated in order to clarify the SAS codes used for each step. Interaction should be included in the primary model if it is significant and not assessed in a separate table, so this has been revised. A robustness analysis using bootstrap method has been added. If no significant treatment*country interaction is observed in the primary model, then the interaction will not be investigated in the robustness analyses on PP population.
24 25 28	3.2.1.2.1 3.2.1.2.2 3.2.1.2.6	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Interaction analyses have been clarified to be checked systematically in the models and analyses by country have been added.
26	3.2.1.2.4	18JUN2018 (v2.0)	26FEB2020 (v3.0)	The reason for non-completion will also be described.
27	3.2.1.2.5	18JUN2018 (v2.0)	26FEB2020 (v3.0)	The times for KM estimates have been revised (e.g. addition of 15h and 18h for time to clear effluent) to be more consistent.
29	3.2.1.2.8	18JUN2018 (v2.0)	26FEB2020 (v3.0)	The proportion of subjects who needed a nasogastric tube to complete preparation will also be tabulated by dose, in addition of overall summary.
29	3.2.1.2.9	18JUN2018 (v2.0)	26FEB2020 (v3.0)	The overall treatment acceptability will be derived as the average of the scores observed at each dose and analysed using a two-way ANOVA.
29	3.2.1.2.10	18JUN2018 (v2.0)	26FEB2020 (v3.0)	The volume taken will also be described. Interaction analysis has been clarified and analysis by country has been added. In addition, analyses by sex, age class and weight class have been added
NA	NA	18JUN2018 (v2.0)	26FEB2020 (v3.0)	New section 3.2.1.3.4 The endpoint “time between the last intake of fluids and the start of colonoscopy procedure” has been added.

33	3.2.2.1	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Causality of SAEs and TEAEs leading to death have been added in the summary table of AEs. Tables with TEAEs with incidence >= 5 % and with TEAEs by decreasing frequency of PT have been added. The summary table of AEs will also be provided by sex, age class and weight class. 95 % CI of proportions will only be displayed in summary tables, and not in the tables by SOC/PT.
34	3.2.2.2	18JUN2018 (v2.0)	26FEB2020 (v3.0)	As no normal range for sulfate is available, corresponding analyses have been removed. The formula for laboratory data standardisation has been specified.
34	3.2.2.3	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Categories for weight, blood pressure and heart variations have been specified.
34	3.2.2.4	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Tolerability will also be described according to use of nasogastric tube, sex, age class and weight class.
36	3.2.5	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Summaries will also be provided by country.
36	3.2.6	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Demography will also be provided by sex, age class and weight class..
38	3.2.8	18JUN2018 (v2.0)	26FEB2020 (v3.0)	All major deviations will be described and not only those having an impact on populations.
40	3.2.15	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Subgroups analyses on country, sex, age class and weight class have been added.
41	5	18JUN2018 (v2.0)	26FEB2020 (v3.0)	Changes from the protocol have been specified, i.e. replication of secondary analysis on PP population, additional subgroup analyses and addition of an endpoint (“time between the last intake of fluids and the start of colonoscopy procedure”).
19	1.4.2.3	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Addition of haematology as other assessment.

20	1.4.3	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Removal of "(except if AE)" in the footnote n of table 5.
23	2.1.2	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Specification that only major deviations impacting analyses will be considered as excluding from the per protocol population.
27	3.2.1.1	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Addition of option first in the proc logistic used for bootstrap to be consistent with the primary model.
30/31	3.2.1.2.3	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Addition of timepoints for the description of time to clear effluent.
36	3.2.1.3.1	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Addition of timepoints for the description of time to first bowel movement.
39	3.2.2.1	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Addition of table on related TEAEs.
39	3.2.2.2	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Removal of "Laboratory data will be displayed in Standard International (SI) units." Since it is specified below. Addition of - the derivation of abnormal status according to normal ranges, - a threshold for eGFR normal values, - a sensitivity analysis of sulfate according to fasting status. Precision that there is no normal range for pH and specific gravity, so standardisation will not be performed and no shift table will be provided.
41	3.2.2.6	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Removal that findings could be reported as AEs.
41	3.2.4	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Addition of a flow chart with the number of subjects in each analysis population.
49	5	26FEB2020 (v3.0)	25AUG2020 (v4.0)	Modification of the per protocol definition.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	Adverse Event
ALT:	Alanine aminotransferase
AST:	Aspartate aminotransferase
ATC:	Anatomic Therapeutic Class
ANOVA:	Analysis of Variance
BBPS:	Boston Bowel Preparation Scale
BMI:	Body Mass Index
BP:	Blood pressure
CBC:	Complete Blood Count
CI:	Confidence Interval
CMH:	Cochran-Mantel-Haenszel
CPK:	Creatine Phosphokinase
CRP:	C reactive protein
eCRF:	Electronic Case Report Form
eGFR:	Estimated Glomerular Filtration Rate
GGT:	Gamma-Glutamyl Transferase
HR:	Heart Rate
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
INR:	International Normalised Ratio
ITT:	Intention-To-Treat
KM:	Kaplan-Meier
LC:	Left colon
LDH:	Lactic Dehydrogenase
MCH:	Mean Cell Haemoglobin
MCHC:	Mean Cell Haemoglobin Concentration
MCV:	Mean Cell Volume
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	Modified Intention-To-Treat
PEG:	PolyEthylene Glycol
PP:	Per Protocol
PT:	Preferred term
RBC:	Red blood cell
RC:	Right colon
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan

SAS®:	Statistical Analysis System®
SD:	Standard Deviation
SI:	Standard International
SOC:	System Organ Class
TC:	Transverse colon
TEAE:	Treatment Emergent Adverse Event
TFL:	Table, figure and listing
V:	Visit
WBC:	White blood cell
WHO-DD:	World Health Organization – Drug dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study purpose

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.

1.2 Study objectives

1.2.1 Primary objective

The primary objective of the study is to demonstrate that Eziclen®/Izinova®, an osmotic sulfate-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.

1.2.2 Secondary objectives

The secondary study objectives are:

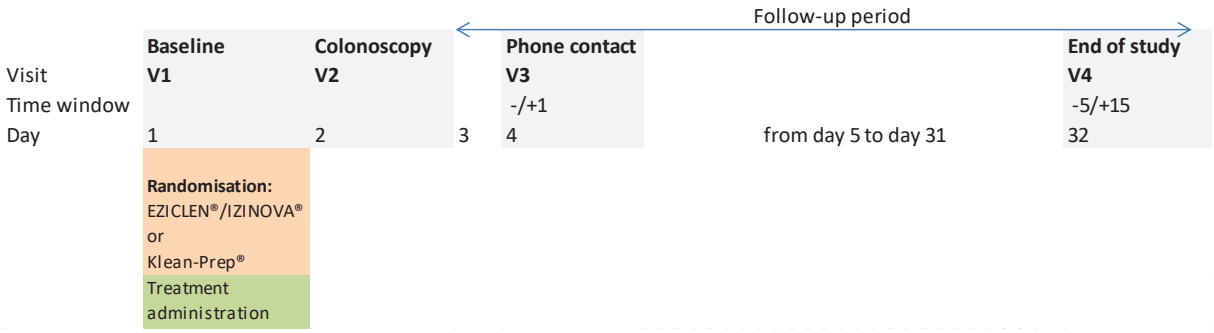
- To compare efficacy of Eziclen®/Izinova® versus Klean-Prep® on overall and segmental cleansing and colonoscopy quality indicators,
- To assess compliance with preparation administration in both study arms,
- To compare safety, acceptability and tolerability of Eziclen®/Izinova® versus Klean-Prep®.

1.3 Study design

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 enroll subjects from around 25 centres. Subjects will be randomised in 2 parallel arms to receive either Eziclen®/Izinova® or Klean-Prep®.

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

Figure 1 Study flow chart



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

At baseline visit (Visit 1), subjects meeting all eligibility criteria will be randomised to receive either Eziclen®/Izinova® or Klean-Prep® solution. The treatment will be administered on the same day (Day 1). After having received either Eziclen®/Izinova® or Klean-Prep® solution, subjects will undergo colonoscopy on the next day (Day 2). Subjects will be contacted by phone on Day 4 and will come on Day 32 for a safety follow-up visit.

1.3.1 Study population

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.

1.3.1.1 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 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, 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

1.3.1.2 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* [1]), 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

1.3.2 Study exposure

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 Investigational Medicinal Product (IMP) intake).

The overall duration of the study will be approximately 13 months (12 months of recruitment + 1 month of follow-up).

1.4 Methods and procedures

1.4.1 Subject identification and allocation to study treatment

All subjects enrolled will 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.

After eligibility is confirmed, at V1 (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 circumstance 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.

1.4.2 Subjects assessments

1.4.2.1 Efficacy assessments

Blinded overall assessment of preparation efficacy will be determined by the colonoscopist upon completion of the examination, based on a 4-point scale. The colonoscopist will score the quality of the bowel preparation using the following Cleansing Score (Table 1).

Table 1 Cleansing Score

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

The primary efficacy will be assessed on the basis of preparation success or failure. The primary efficacy variable is the proportion of subjects with a successful overall preparation.

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

The secondary efficacy endpoints are summarised below (Table 2):

Table 2 Secondary Endpoints and Evaluations

Endpoint	Timepoint	Evaluation
Colon cleansing	V2 (Colonoscopy)	Cleansing Score assessed on 4 levels (4-point scale, see Table 1).
Overall and segmental cleansing assessed by Boston Bowel Preparation Scale (BBPS)	V2 (Colonoscopy)	BBPS (see Table 3) Overall score [1]. Segmental scores (left colon (LC), transverse colon (TC), right colon (RC)).
Time to clear effluent (hours)	V1 (Treatment)	Time between first intake of prescription and first clear watery stool.
Complete procedure	V2 (Colonoscopy)	Number (%) of complete procedures defined as procedures that reached the caecum.
Time to caecal intubation (minutes)	V2 (Colonoscopy)	Time between the colonoscope introduction and the time to reach caecum.
Duration of examination (minutes)	V2 (Colonoscopy)	Time between the caecum is reached and the withdrawal of the colonoscope.
Need for rescue treatment because of inadequate preparation intake.	V2 (before colonoscopy)	Number (%) of procedures that need a rescue treatment (saline enema).
Treatment acceptability	V1 (Treatment)	Level of acceptability of treatment assessed using a 5-point Treatment Acceptability Questionnaire (see Table 4).
Need for nasogastric tube	V1 (Treatment)	Number (%) of subjects who need a nasogastric tube to complete preparation.
Treatment compliance	V1 (Treatment)	Percentage of volume of fluid taken relative to the planned volume of fluid to be taken
Time between the last intake of fluids and the start of colonoscopy procedure (hours)	V1 (Treatment) and V2 (Colonoscopy)	Time between the end of treatment administration and the start of colonoscopy.

The overall and segmental cleansing as assessed by BBPS [1] is presented in Table 3.

Table 3 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

Scores for the right colon (RC), transverse colon (TC) and left colon (LC) will be collected. Scores per segment will be summed to provide overall cleansing score.

The Treatment Acceptability Questionnaire will be completed by the caregiver or subject after the subject ends the intake of preparation. Caregivers will be asked to rate subject acceptability using the following categories (Table 4).

Table 4 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

The compliance will be assessed from the treatment questionnaire which will be completed by the caregiver or subject after the subject ends the intake 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.

1.4.2.2 Safety assessments

- Adverse events (AEs) occurring during the study, from signature of informed consent up to 30 days after colonoscopy (collected at Visit 4 Day 32 -5/+15), and with the following categorizations:
  - Seriousness (Yes/No),
  - Intensity (Mild/Moderate/Severe),
  - Causality (i.e. relationship to study treatment, as Related/Not related).
- Tolerability by a Symptom Scale after each dose of treatment. Subjects/caregivers will rate the preparation related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, with 1=no symptom, 2=mild, 3=bothersome, 4=distressing and 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: (systolic and diastolic) blood pressure (BP) and heart rate (HR) will be assessed with an automated device so that measurements are independent of the observer. BP and HR will be recorded in standing position and after 5 minutes rest in supine position at V1, after 5 minutes rest in supine position at V2 and V4. Absolute values and change from Baseline (V1) will be analysed. Body temperature and weight will be recorded at V1, V2 and V4.
- Local laboratory data at V1, V2 and V4:
  - Serum 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, phosphate, bicarbonate), alkaline phosphatase, albumin, total protein, C reactive protein (CRP), uric acid, creatinine clearance, eGFR (calculated in the eCRF using the Schwartz bedside equation [1]: eGFR = 0.41 * height (cm)/S_{cr} (mg/dl), where S_{cr} is the serum creatinine) and osmolality.

- Urinalysis by dipstick including pH, protein, ketones, bilirubin, blood, urobilinogen, nitrites, leukocytes, glucose and specific gravity microscopic examination.

• Blood and urine sulfates dosages by central laboratory at V1, V2 and V4.

1.4.2.3 Other assessments

Haematology collected at V1 as baseline characteristics.

1.4.2.4 Withdrawal/discontinuation

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, 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 of the protocol.

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 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 V2.

1.4.3 Schedule of assessments

Table 5 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 sulfates[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		X		

Study Period	Baseline/ Treatment	Colonoscopy	Phone contact	End of Study (or in case of Early Withdrawal*)
unblinded site member				
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, phosphate, 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 sulfate 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 6 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®.

1.4.4 Planned sample size

The primary aim of the study is to show that Eziclen®/Izinova® is non-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.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Efficacy

2.1.1 Intention-To-Treat population (ITT)

The ITT population is:

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.

2.1.1 Modified Intention-To-Treat population (mITT)

The mITT population is:

All randomised subjects who received even a partial dose of study treatment and produced a primary efficacy assessment.

Subjects will be assessed according to their randomised treatment, regardless of the treatment they receive.

2.1.2 Per Protocol population (PP)

The PP population is:

All subjects in the ITT population, who have undergone the colonoscopy procedure and for whom no major protocol violation/deviation impacting analyses (as defined in the Protocol Deviation Document) occurred.

2.2 Safety

The safety population is:

All randomised subjects with at least a partial dose of study medication.

Subjects will be assessed according to the treatment received.

2.3 Pharmacokinetics

Not applicable.

2.4 Other populations

2.4.1 Screened population

The screened population is:

All subjects screened (i.e. who signed the informed consent).

2.5 Primary populations

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.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline [3], will be based on the pooled data from the individual study sites, unless otherwise stated, and will be performed by Biotrial Biometrics, France, managed by the sponsor's Biometry Department.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9.4 or higher) [4]

3.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the proportion of subjects with a successful overall preparation (i.e. graded as excellent (4) or good (3) based on a 4-point scale).

3.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are:

- the need to place a nasogastric tube to complete preparation,
- the time to clear effluent (from first intake of preparation), as reported by the subject,
- the need for rescue treatment (saline enema) because of inadequate preparation,
- the colon cleansing scores assessed by the 4-point scale (poor, fair, good, excellent),
- the overall and segmental cleansing scores assessed by BBPS,
- the time to caecal intubation (from colonoscope introduction to caecal intubation),
- the duration of examination, measured by colonoscope withdrawal time from caecum,
- the procedure documented as completed (procedures that reached the caecum),
- the treatment compliance: volumes of fluids measured by the caregiver and reported in the treatment questionnaire of subject's leaflet during treatment administration,
- the treatment acceptability, assessed by a Treatment Acceptability Questionnaire completed by the caregiver or the subject at the time of intake using a 5-point scale questionnaire to be filled in immediately after dosing,
- the time between the last intake of fluids and the start of colonoscopy procedure.

3.1.3 Safety endpoints

The safety endpoints are:

- Collection of adverse events (AEs) (for up to 30 days following the day of colonoscopy (collected at Visit 4 Day 32 -5/+15));
- Tolerability of the preparation by a Symptom Scale after each dose of treatment rated by the subjects on related symptoms after intake (stomach cramping, stomach bloating and nausea) on a paediatric 5-point scale, ranging from 1=no symptom 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 temperature, systolic and diastolic BP and HR;
- Local laboratory data: serum and urinary biochemistry, at baseline, at colonoscopy and at the end of study;
- Blood and urine sulfates assessed at central laboratory.

3.1.4 Multiplicity

No adjustment for multiple testing is planned in this study, since 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, so that the second test (superiority) will only be considered if the first test (non-inferiority) is accepted.

3.1.5 Significance testing and estimation

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

A two-sided 95 % confidence interval (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® will be 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® will be proven to be superior to Klean-Prep®.

The secondary endpoints will be tested for descriptive purpose only.

3.2 Analysis methods

Descriptive statistics will be presented as follows:

- Continuous variables: number of observations, number of missing data, mean, standard deviation (SD), median, quartiles, minimum and maximum;
- Dichotomous or categorical variables: frequency and percentage of each of the categories and number of missing data.

All study data will be at least presented in listings.

3.2.1 Efficacy

The primary efficacy analysis will be performed on the mITT population as well as on the PP population to assess the robustness of the results. The secondary efficacy analyses will be performed on the ITT population and repeated on the mITT and PP if they differ from ITT from more than 10 %. The other efficacy analyses will be performed on the ITT population and repeated on the mITT if it differs from ITT from more than 10 %.

3.2.1.1 Primary efficacy analyses

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.

The two hypothesis tests are hierarchically structured so that the second test (superiority) will only be considered if the first test (non-inferiority) is accepted. 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 mITT population and repeated on the PP population in order to assess the robustness of the results.

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 colon cleansing score,
- 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 % CI using the standard Wald asymptotic CI using the following SAS code:

```
proc freq data=ADCC(where=(PARAM='Successful overall preparation' and
MITTFL='Y'));
        table AVALC / missing binomial(level='Yes' cl=wald);
       by TRTP;
run;
```

The primary efficacy endpoint will be analysed using a logistic regression model including treatment and country as covariates as well as the interaction between treatment and country if it is significant (i.e. $p < 0.10$, as interaction tests have low power) using the following SAS code providing the adjusted proportions with their 95 % CI thank to ilink option, and with the option firth in the model with interaction since there might otherwise be a quasi-complete separation of data points affecting the validity of the model:

```
proc logistic data=ADCC(where=(PARAM='Successful overall preparation' and
MITTFL='Y'));
    class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country') /
    param=glm;
    model AVALC(EVENT='Yes') = TRTP COUNTRYC TRTP*COUNTRYC /
    link=logit firth;
    lsmeans TRTP / cl ilink;
    ods output lsmeans=lsm ModelANOVA=TestInter;
run;
```

N.B.: TRTP*COUNTRYC, firth and ModelANOVA=TestInter will be removed if the interaction is not significant.

The formal hypothesis test result (p-value) for treatment difference will be presented together with a two-sided 95 % CI for the treatment 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 treatment difference and its p-value assessed for -15 % margin will be estimated using the

following SAS code, since the logistic procedure does not provide adjusted treatment differences:

```
proc freq data=ADCC(where=(PARAM='Successful overall preparation' and MITTFL='Y'));
    table TRTP / nopercent norow nocum;
    ods output OneWayFreqs=TRTfreq;
run;
data estimates;
    merge TRTfreq lsm;
    by TRTP;
    AVALC="N"; Count=Frequency*(1-Mu); output;
    AVALC="Y"; Count=Frequency*Mu; output;
    keep TRTP Frequency Mu AVALC Count;
run;
proc freq data=estimates order=data;
    table TRTP*AVALC / alpha=0.05 riskdiff(noninf margin=0.15 column=2);
    weight Count;
    ods output PdiffNoninf=NonInf;
run;
```

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® will be proven to be superior to Klean-Prep®. The following SAS code will be used to get the superiority p-value:

```
proc freq data=estimates order=data;
    table TRTP*AVALC / alpha=0.05 riskdiff(sup column=2);
    weight Count;
    ods output PdiffSup=Sup;
run;
```

A robustness analysis of primary efficacy results will be assessed by repeating the primary analysis on the PP population.

Furthermore, the robustness of the results will be assessed by using another SAS procedure in the mITT, since the adjusted difference cannot be assessed directly from the proc logistic inducing a potential bias. Then the SAS procedure genmod will be used with identity link including treatment and country as covariates, using the following example of SAS code:

```
proc genmod data=ADCC(where=(PARAM='Successful overall preparation' and MITTFL='Y'));
    class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country');
    model AVALC(EVENT='Yes') = TRTP COUNTRYC / link=identity;
    lsmeans TRTP / diff cl;
run;
```

No p-value will be displayed for the genmod model, since this would not be equivalent to the ones provided for the logistic procedure analysis.

In addition, the robustness of the results will be assessed in the mITT population by repeating the procedure logistic and estimating the 95 % CI of the treatment difference using the bootstrap method:

- The adjusted proportions will be estimated using the proc logistic model;
- 10’000 random samples will be generated using a proc surveyselect from the observed data with treatment and country as stratification and with seed=111;
- The adjusted proportions for each sample will be estimated using the same proc logistic model by replicate;
- The treatment differences will be derived for each sample;
- The 2.5 and 97.5 percentiles of the 10’000 estimated treatment differences will be considered for the 95 % CI of the treatment difference.

The following SAS code will be used:

```
proc logistic data=ADCC(where=(PARAM='Successful overall preparation' and MITTFL='Y'));
        class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country') / param=glm;
        model AVALC(EVENT='Yes') = TRTP COUNTRYC / link=logit firth;
        lsmeans TRTP / cl ilink;
        ods output lsmeans=lsm;
run;
proc transpose data=lsm out=_lsm;
        var Mu;
        id TRTP;
run;
data diff;
        set _lsm;
        diff = EZICLEN – KLEAN-PREP;
run;
proc surveyselect data=ADCC(where=(PARAM='Successful overall preparation' and MITTFL='Y')) out=samples method=urs samprate=1 rep=10000 outhits seed=111;
        strata TRTP COUNTRYC;
run;
proc sort data=samples; by replicate; run;
proc logistic data=samples;
        by replicate;
        class replicate TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country') / param=glm;
        model AVALC(EVENT='Yes') = TRTP COUNTRYC / link=logit;
        lsmeans TRTP / cl ilink;
        ods output lsmeans=lsm_boot(keep=replicate TRTP Mu);
run;
```

```
proc sort data=lsm_boot; by replicate; run;
proc transpose data=lsm_boot out=_lsm_boot;
        var Mu;
        by replicate;
        id TRTP;
run;
data final;
        set _lsm_boot;
        diff = EZICLEN - KLEAN-PREP;
run;
proc sort data=final; by diff; run;
proc univariate data=final noprint;
        var diff;
        output out=ci95(rename=(Q2_5=Lower Q97_5=upper Q50=median)) pctlpre=Q
        pctlpts=2.5 50 97.5;
run;
```

No p-value will be displayed for this robustness analysis.

Finally, primary efficacy results will be repeated in the mITT by country using the main model with the treatment * country interaction in order to get the treatment effect by country as follows:

```
proc logistic data=ADCC(where=(PARAM='Successful overall preparation' and
MITTFL='Y'));
        class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country') /
        param=glm;
        model AVALC(EVENT='Yes') = TRTP COUNTRYC TRTP*COUNTRYC /
        link=logit firth;
        lsmeans TRTP*COUNTRYC / cl ilink;
run;
```

The adjusted proportions by country with their 95 % CI and the treatment difference with their 95 % CI derived using proc freq as above by country will be presented, but p-values will not be displayed.

And primary analysis will also be repeated in the mITT by age class, weight class and sex using the main model with the treatment * country interaction if it is significant in the primary model, as well as the treatment * subgroup interaction as follows:

```
proc logistic data=ADCC(where=(PARAM='Successful overall preparation' and
MITTFL='Y'));
        class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country')
        SUBGROUP(ref='First class') / param=glm;
        model AVALC(EVENT='Yes') = TRTP COUNTRYC TRTP*COUNTRYC
        TRTP*SUBGROUP / link=logit firth;
        lsmeans TRTP*SUBGROUP / cl ilink;
run;
```

The adjusted proportions by subgroup with their 95 % CI and the treatment differences with their 95 % CI will be presented, but p-values will not be displayed.

3.2.1.2 Secondary efficacy analyses

Analysis of secondary efficacy endpoints will be performed on the ITT population and could be duplicated on mITT if there is a difference of more than 10% of subjects between ITT and mITT.

3.2.1.2.1 Colon cleansing score

The colon cleansing scores will be assessed by the 4-point scale (see Table 1) and will be presented by treatment group using descriptive summary statistics (mean, SD, median, quartiles and ranges) and using a two-way analysis of variance (ANOVA) including treatment and country as well as the interaction between treatment and country, if it is significant (i.e. $p < 0.10$), as covariates using the following SAS code:

```
proc mixed data=ADCC(where=(PARAM='Cleansing score' and ITTFL='Y'));
        class TRTP COUNTRYC;
        model AVAL = TRTP COUNTRYC TRTP*COUNTRYC;
        lsmeans TRTP / diff cl;
run;
```

The adjusted mean scores, the adjusted treatment difference with their 95 % CI and the p-value of difference will be summarised.

In addition, this analysis will also be produced per country so that mean scores and the estimated treatment differences will also be provided per country using the following SAS code.

```
proc mixed data=ADCC(where=(PARAM='Cleansing score' and ITTFL='Y'));
        class TRTP COUNTRYC;
        model AVAL = TRTP COUNTRYC TRTP*COUNTRYC;
        lsmeans TRTP*COUNTRYC / diff cl;
run;
```

3.2.1.2.2 Overall and segmental cleansing scores assessed by BBPS

The overall (LC + TC + RC) and segmental (LC, TC, RC) cleansing scores will be assessed by BBPS (see Table 3) and will be presented by treatment group using descriptive summary statistics (mean, SD, median, quartiles and ranges) and using a two-way analysis of variance (ANOVA) including treatment and country as well as the interaction between treatment and country, if it is significant (i.e. $p < 0.10$), as covariates using the following SAS code:

```
proc mixed data=ADCC(where=(PARAM='BBPS - Global Score'/'BBPS - Left colon
score'/'BBPS - Transverse colon score'/'BBPS - Right colon score' and ITTFL='Y'));
        class TRTP COUNTRYC;
        model AVAL = TRTP COUNTRYC TRTP*COUNTRYC;
        lsmeans TRTP / diff cl;
run;
```

The adjusted mean scores, the adjusted treatment differences with their 95 % CI and the p-value of difference will be summarised.

In addition, this analysis will also be produced per country so that mean scores and the estimated treatment differences will also be provided per country using the following SAS code.

```
proc mixed data=ADCC(where=(PARAM='BBPS - Global Score'/'BBPS - Left colon score'/'BBPS - Transverse colon score'/'BBPS - Right colon score' and ITTFL='Y'));
    class TRTP COUNTRYC;
    model AVAL = TRTP COUNTRYC TRTP*COUNTRYC;
    lsmeans TRTP*COUNTRYC / diff cl;
run;
```

The proportion of subjects with successful overall preparation, assessed by the total score of the BBPS, will also be presented. Successful overall preparation will be defined based on a global BBPS score ≥ 6 for the sum of the 3 segments (right, transverse and left colon) and will be presented by treatment group using frequency count with two-sided 95 % CI and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The general association statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data= ADCC(where=(PARAM='Successful overall preparation BBPS' and ITTFL='Y'));
    table COUNTRYC*TRTP*AVALC / CMH;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

3.2.1.2.3 Time to clear effluent

The time to clear effluent as reported by the subject as the time between first intake of prescription and first clear watery stool will be assessed and will be analysed using survival methods.

Table 7 specifies the event and censoring dates to be used in the analysis of time to clear effluent.

Table 7 Time to Clear Effluent (hours)

Event	Time of event	Outcome
Clear watery stools	Time of clear watery stools	Event
No clear watery stools with colonoscopy	Time of colonoscope introduction	Censored
No clear watery stools without colonoscopy	Time of start of treatment + 12h	Censored

The distribution of time to clear effluent will be estimated using the Kaplan-Meier (KM) product limit method. The results will be presented in a summary table and a KM plot will also be constructed.

The summary table will present by treatment group the numbers and percentages of subjects with occurrence of clear watery stool and the numbers and percentages of censored subjects. The summary will also include the median time to clear effluent as well as the 25th and 75th

percentiles with their two-sided 95 % CI, the percentage and 95 % CIs of subjects who had clear watery stool at 2, 3, 4, 5, 6, 9, 12, 15, 18 and 24 hours from KM estimates.

Confidence intervals for median time to clear effluent as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982) [5], which is the default method within SAS® version 9 and higher.

Kaplan-Meier curves will be constructed by treatment group and will display the number of subjects at risk at 1, 1.5, 2, 2.5, 3, 3.5, 6, 9, 12, 15, 18 and 24 hours.

In addition, the treatment difference will be tested using a Cox proportional hazards model adjusted on country and the association with treatment will be further explored by presenting separate KM plots for each country.

The SAS Phreg procedure will be used as follows:

```
Proc Phreg Data=ADTTE(where=(PARAMCD='Time to Clear Effluent (hours)' and
ITTFL='Y'));
        Class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country');
        Model AVAL*CNSR(1) = TRTP COUNTRYC / Ties = EXACT;
Run;
```

3.2.1.2.4 Complete procedure

The proportion of complete procedure (defined as procedures (i.e. colonoscopies) that reached the caecum) will be assessed. It will be tabulated by treatment group using frequency count with two-sided 95 % CI and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The general association statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADPR(where=(PRTRT='COLONOSCOPY' and AVISITN=2 and
ITTFL='Y'));
        table COUNTRYC*TRTP*PROCCUR / CMH;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

The reasons for non-completion will also be presented.

3.2.1.2.5 Time to caecal intubation

The time to caecal intubation (from colonoscope introduction to caecal intubation) will be assessed and will be analysed using survival methods on subjects who performed colonoscopy.

Table 8 specifies the event and censoring dates to be used in the analysis of time to clear effluent.

Table 8 Time to caecal intubation (minutes)

Event	Time of event	Outcome
Caecal intubation	Time of caecal intubation	Event
Procedure (i.e. colonoscopy) did not reach the caecum	Time of withdrawal of colonoscope	Censored

The distribution of time to caecal intubation will be estimated using the Kaplan-Meier (KM) product limit method. The results will be presented in a summary table and a KM plot will also be constructed.

The summary table will present by treatment group the numbers and percentages of subjects with occurrence of caecal intubation and the numbers and percentages of censored subjects. The summary will also include the median time to caecal intubation as well as the 25th and 75th percentiles with their two-sided 95 % CI, the percentage and 95 % CIs of subjects who had caecal intubation at 5, 10, 15, 20, 25, 30, 45 and 60 minutes from KM estimates.

Confidence intervals for median time to caecal intubation as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982) [5], which is the default method within SAS® version 9 and higher.

Kaplan-Meier curves will be constructed by treatment group and will display the number of subjects at risk at 5, 10, 15, 20, 25, 30, 45 and 60 minutes.

In addition, the treatment difference will be tested using a Cox proportional hazards model adjusted on country and the association with treatment will be further explored by presenting separate KM plots for each country.

The SAS Phreg procedure will be used as follows:

```
Proc Phreg Data=ADTTE(where=(PARAMCD=’Time to caecal intubation' and ITTFL='Y'));
        Class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country');
        Model AVAL*CNSR(1) = TRTP COUNTRYC / Ties = EXACT;
Run;
```

3.2.1.2.6 Duration of examination

The duration of examination (in minutes), measured by the difference between the time of caecum intubation and the time of withdrawal of the colonoscope, will be assessed. Subjects for whom the caecum was not reached will be excluded from this analysis. The results will be presented by treatment group using descriptive summary statistics (mean, SD, median, quartiles and ranges) and using a two-way ANOVA including treatment and country as well as the interaction between treatment and country, if it is significant (i.e. $p < 0.10$), as covariates using the following SAS code:

```
proc mixed data=ADCC(where=(PRTRT=’COLONOSCOPY’ and AVISITN=2 and ITTFL='Y'));
    class TRTP COUNTRYC;
    model ADUREXA = TRTP COUNTRYC TRTP*COUNTRYC;
    lsmeans TRTP / diff cl;
run;
```

The adjusted mean durations of examination, the adjusted treatment difference with their 95 % CI and the p-value of difference will be summarised.

In addition, this analysis will also be produced per country so that mean durations and the estimated treatment differences will also be provided per country using the following SAS code.

```
proc mixed data=ADCC(where=(PRTRT='COLONOSCOPY' and AVISITN=2and ITTFL='Y'));
    class TRTP COUNTRYC;
    model ADUREXA = TRTP COUNTRYC TRTP*COUNTRYC;
    lsmeans TRTP*COUNTRYC / diff cl;
run;
```

3.2.1.2.7 Rescue treatment

The proportion of procedures that need a rescue treatment (saline enema) because of inadequate preparation intake will be assessed. It will be tabulated by treatment group using frequency count with two-sided 95 % CI and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The general association statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADCM(where=(CMCAT='RESCUE MEDICATION' and CMTRT='ENEMA' and ITTFL='Y'));
    table COUNTRYC*TRTP*CMOCCUR / CMH;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

3.2.1.2.8 Need for a nasogastric tube

The proportion of subjects who needed a nasogastric tube to complete preparation will be assessed and the reason for placing it will be collected. They will be tabulated by treatment group using frequency count with two-sided 95 % CI and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The general association statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADEX(where=(EXTRT=' EZICLEN/IZINOVA' and ITTFL='Y'));
    table COUNTRYC*TRTP*NASOTUBE / CMH;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

The proportion of subjects who needed a nasogastric tube to complete preparation will also be tabulated by dose.

3.2.1.2.9 Treatment acceptability

The treatment acceptability at the time of intake after dose 1 and after dose 2 will be assessed by a Treatment Acceptability Questionnaire completed by the caregiver or the subject using a

5-point scale questionnaire (see Table 4). It will be tabulated for each dose and overall (by taking the average of the 2 doses then considered as a score as follows: 1= Very badly accepted/unacceptable, 2= Badly but accepted, 3= Neither good nor bad, 4= Well accepted and 5= Very well accepted) by treatment group.

The acceptability for each dose will be assessed using frequency count with two-sided 95 % CI and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The row mean scores differ statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADQS(where=(QSCAT='TREATMENT ACCEPTABILITY QUESTIONNAIRE' and PARAMCD in ('TRTA011','TRTA012') and ITTFL='Y'));
    table COUNTRYC*TRTP*QSORRES / CMH;
    by QSGRPID;
run;
```

The p-value of difference will be summarised.

The overall acceptability will be presented by treatment group using descriptive summary statistics (mean, SD, median, quartiles and ranges) and using a two-way ANOVA including treatment and country as well as the interaction between treatment and country, if it is significant (i.e. $p < 0.10$), as covariates using the following SAS code:

```
proc mixed data=ADQS(where=(QSCAT='TREATMENT ACCEPTABILITY QUESTIONNAIRE' and PARAMCD='TRTA01' and ITTFL='Y'));
    class TRTP COUNTRYC;
    model COMPLIPCT = TRTP COUNTRYC TRTP*COUNTRYC;
    by ASPID;
    lsmeans TRTP / diff cl;
run;
```

The adjusted mean score, the adjusted treatment difference with their 95 % CI and the p-value of difference will be summarised.

3.2.1.2.10 Treatment compliance

According to the instructions of use provided in the prescription, subjects should get for Eziclen®/Izinova® 750 mL of preparation followed by an additional 750 mL of water at first and second dose, that is to say a total volume of 2250 mL, and for Klean-Prep® 70 mL/kg of preparation according to the weight split into 2 doses with a maximum global volume administered of 4000 mL (2000 mL per dose). The volumes taken will be presented by treatment group using descriptive summary statistics (mean, SD, median, quartiles and ranges). No comparison will be performed since treatment administration schemes are different.

The treatment compliance will be assessed as the percentage of volume of fluid taken relative to the planned volume of fluid to be taken using the volumes of fluids measured by the caregiver and reported in the treatment questionnaire of subject's leaflet during treatment administration by dose and overall for the preparation for Klean-Prep® and for the preparation, the water and the total for Eziclen®/Izinova®. Then the percentage of compliance will be presented by treatment group using descriptive summary statistics (mean,

SD, median, quartiles and ranges) and using a two-way ANOVA including treatment and country as well as the interaction between treatment and country, if it is significant (i.e. $p < 0.10$), as covariates using the following SAS code:

```
proc mixed data=ADEX(where=(EXCAT='COMPLIANCE' and EXSCAT='Overall' and ITTFL='Y'));
    class TRTP COUNTRYC;
    model COMPLIPCT = TRTP COUNTRYC TRTP*COUNTRYC;
    by ASPID;
    lsmeans TRTP / diff cl;
run;
```

The adjusted mean compliances, the adjusted treatment difference with their 95 % CI and the p-value of difference will be summarised.

In addition, this analysis will also be produced per country so that mean compliances and the estimated treatment differences will also be provided per country using the following SAS code.

```
proc mixed data= ADEX(where=(EXCAT='COMPLIANCE' and EXSCAT='Overall' and ITTFL='Y'));
    class TRTP COUNTRYC;
    model COMPLIPCT = TRTP COUNTRYC TRTP*COUNTRYC;
    lsmeans TRTP*COUNTRYC / diff cl;
run;
```

Moreover, this analysis will also be produced per sex, age class and weight class, so that mean compliances and the estimated treatment differences will also be provided per subgroup using the following SAS code and adding the treatment*country interaction if it is significant.

```
proc mixed data= ADEX(where=(EXCAT='COMPLIANCE' and EXSCAT='Overall' and ITTFL='Y'));
    class TRTP COUNTRYC SUBGROUP;
    model COMPLIPCT = TRTP COUNTRYC SUBGROUP TRTP*SUBGROUP;
    lsmeans TRTP*SUBGROUP / diff cl;
run;
```

Additionally, a subject will be considered as compliant with the instructions of use provided in the prescription if he/she drinks the whole preparation (volume = 100 %). The proportion of subjects compliant with the instructions of use provided in the prescription will be presented using summary statistics with the 95 % CI by treatment group and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The general association statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADEX(where=(EXCAT='COMPLIANCE' and EXSCAT='Overall' and ITTFL='Y'));
    table COUNTRYC*TRTP*COMPLI / CMH;
    by ASPID;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

Finally, the compliance will be presented by categories (100 %,]100-75],]75-50] and < 50 %). The proportion of subjects in each category will be presented using summary statistics with the 95 % CI by treatment group and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The row mean scores differ statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADEX(where=(EXCAT='COMPLIANCE' and EXSCAT='Overall' and
ITTFL='Y'));
    table COUNTRYC*TRTP*COMPLICL / CMH;
    by ASPID;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

The percentage of compliance, the proportion of patients considered as compliant and the compliance in categories will be described after each dose and overall. For the Eziclen/Izinova treatment group, the compliance will be also described separately for active treatment and hydration after each dose and overall.

3.2.1.3 Other efficacy analyses

Analysis of other efficacy endpoints will be performed on the ITT population.

3.2.1.3.1 Time to first bowel movement

The time to first bowel movement defined as the time between first intake of prescription and first bowel movement will be assessed and analysed using survival methods.

Table 9 specifies the event and censoring dates to be used in the analysis of time to first bowel movement.

Table 9 Time to First Bowel Movement (hours)

Event	Time of event	Outcome
First bowel movement	Time of first bowel movement	Event
No bowel movement with colonoscopy	Time of colonoscope introduction	Censored
No bowel movement without colonoscopy	Time of first intake of prescription + 12 hours	Censored

The distribution of time to first bowel movement will be estimated using the Kaplan-Meier (KM) product limit method. The results will be presented in a summary table and a KM plot will also be constructed.

The summary table will present by treatment group the numbers and percentages of subjects with occurrence of first bowel movement and the numbers and percentages of censored subjects. The summary will also include the median time to first bowel movement as well as the 25th and 75th percentiles with their two-sided 95 % CI, the percentage and 95 % CIs of subjects who had first bowel movement at 1, 1.5, 2, 2.5, 3, 3.5, 6, 9, 12, 15 and 18 hours from KM estimates.

Confidence intervals for median time to first bowel movement as well as the 25th and 75th percentile CIs will be calculated using the method of Brookmeyer and Crowley (1982) [5], which is the default method within SAS® version 9 and higher.

Kaplan-Meier curves will be constructed by treatment group and will display the number of subjects at risk at 1, 1.5, 2, 2.5, 3, 3.5, 6, 9, 12, 15 and 18 hours.

In addition, The treatment difference will be tested using a Cox proportional hazards model adjusted on country and the association with treatment will be further explored by presenting separate KM plots for each country.

The SAS Phreg procedure will be used as follows:

```
Proc Phreg Data=ADTTE(where=(PARAMCD='Time to first bowel movement' and ITTFL='Y'));
    Class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country');
    Model AVAL*CNSR(1) = TRTP COUNTRYC / Ties = EXACT;
Run;
```

3.2.1.3.2 Wake-up during the night to have a bowel movement

The proportion of patients who wake-up during the night to have a bowel movement will also be tabulated by treatment group using frequency count with two-sided 95 % CI and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The general association statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADCE(where=(CETERM='NIGHTLY BOWEL MOVEMENT' and ITTFL='Y'));
    table COUNTRYC*TRTP*CEOCCUR / CMH;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

3.2.1.3.3 Satisfaction

The satisfaction will be also assessed through the question "If it was necessary, would you agree to undergo preparation with this product again?". It will also be tabulated by treatment group using frequency count with two-sided 95 % CI and analysed using Cochran-Mantel-Hænszel (CMH) chi-square for the proportions adjusting for country effect. The general association statistic will be used to assess the test significance.

The SAS Freq procedure will be used as follows:

```
proc freq data=ADQS(where=(QSTEST='AGREE TO TAKE PRODUCT AGAIN' and ITTFL='Y'));
    table COUNTRYC*TRTP*QSORRES / CMH;
run;
```

The difference of proportions with the 95 % CI and p-value will be summarised.

3.2.1.3.4 Time between the last intake of fluids and the start of colonoscopy procedure

The time between the last intake of fluids and the start of colonoscopy procedure will be presented by treatment group using descriptive summary statistics (mean, SD, median, quartiles and ranges) and using a two-way analysis of variance (ANOVA) including treatment and country as well as the interaction between treatment and country, if it is significant (i.e. $p < 0.10$), as covariates using the following SAS code:

```
proc mixed data=ADEX(where=(PARAM='Time between the last intake of fluids and the start of colonoscopy procedure' and ITTFL='Y'));
    class TRTP COUNTRYC;
```

```
        model AVAL = TRTP COUNTRYC TRTP*COUNTRYC;
        lsmeans TRTP / diff cl;
    run;
```

The adjusted mean times, the adjusted treatment difference with their 95 % CI and the p-value of difference will be summarised.

In addition, this analysis will also be produced per country so that mean scores and the estimated treatment differences will also be provided per country using the following SAS code.

```
    proc mixed data=ADEX(where=(PARAM='Time between the last intake of fluids and
    the start of colonoscopy procedure' and ITTFL='Y'));
        class TRTP COUNTRYC;
        model AVAL = TRTP COUNTRYC TRTP*COUNTRYC;
        lsmeans TRTP*COUNTRYC / diff cl;
    run;
```

3.2.2 Safety

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

3.2.2.1 Adverse events

All AEs will be coded according to MedDRA (last version used for coding during the study course) and will be classified by MedDRA preferred term (PT) and system organ class (SOC). AE listings will be presented by subject, SOC and PT for all AEs, serious AEs (SAEs) and AEs leading to withdrawal on the safety population.

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.

An overall summary table of all AEs will be presented with the number of AEs and the numbers and percentage of subjects with exact 95 % CI for each of the following categories:

- Any AEs,
- Any SAEs,
- Causality of SAEs,
- Any TEAEs,
- Intensity of TEAEs,
- Causality of TEAEs,
- Causality and intensity of TEAEs,
- Any TEAEs leading to death,
- Any TEAEs leading to withdrawal.

In the event of multiple AEs being reported by the same subject, each subject is counted for each intensity level, each causality level or each intensity and causality combined level. That means that the total number of subjects for all levels of intensity/causality might be higher

than the overall number of subjects with at least one AE. Related adverse events are those events with causality missing or related.

Incidence by SOC/PT of all reported TEAEs, related TEAEs, SAEs and TEAEs leading to withdrawal of study medication will be tabulated by treatment group and overall. In addition, summary tables by SOC/PT will present TEAEs by maximum intensity and drug relationship and will present TEAEs with incidence >= 2 %. And a summary table will present TEAEs by decreasing frequency of PT.

In the event of multiple occurrence of the same AE (same PT) being reported by the same subject, the maximum intensity (severe > missing > moderate > mild) and the most serious causality (related > not related) for each concerned PT will be chosen.

Moreover, the summary table will be duplicated by sex, age class and weight class, as well as the summary table of the incidence of TEAEs by SOC and PT.

Additionally, lesions suspected to be caused by colonic lavage (identified during the potential histological examinations of taken colonic biopsy specimens) will be recorded as AEs with the mention "suspected to be caused by colonic lavage" in the verbatim term by the investigator. The occurrence (Yes/No) of such AEs will be summarised for the treated subjects for whom the colonoscopy was done by treatment group and overall as well as the incidence by SOC/PT. The result of the biopsy will be listed.

3.2.2.2 Laboratory data

Laboratory data (haematology, biochemistry, and urinalysis) will be collected locally, while urine and blood sulfates will be assessed centrally. They will be listed in SI units and abnormal values will be derived using original normal ranges when available rather than using the investigator assessment and flagged (High [H], Low [L], clinically significant [C]), where applicable.

For eGFR, a threshold will be used and values ≥ 75 mL/min/1.73 m² will be considered as normal, while the other ones will be considered as low.

Any unscheduled laboratory assessments will be flagged [U] in the listings.

A listing will present all values for a subject with at least one clinically significant abnormal laboratory value for biochemistry and urinalysis.

The baseline will be defined as the last measurement collected prior to the first dose of study drug.

As more than one laboratory will be involved in the study for the measurement of laboratory values, a standardisation method will be required in order to take into account the multiple reference ranges [6] for haematology, biochemistry, and urinalysis parameters with normal ranges. The site which has analysed the largest number of blood samples will be used as the reference site. The following formula will be used:

$$Standardised\ value = L_R + (x - L_X)\frac{U_R - L_R}{U_X - L_X}$$

With L_R the reference site lower limit, U_R the reference site upper limit, L_X the local site lower limit, U_X the local site upper limit and x the non standardised value assessed in the local laboratory.

If a standardised value is negative it will be replaced by 0.

For pH and specific gravity no normal range is available, so no standardisation will be applied and no shift table will be provided.

For continuous urinalysis data and biochemistry, summary statistics will be presented by treatment group at each scheduled assessment for actual values and changes from baseline. Shift tables (based on local assessment) from baseline to each post baseline visit will be presented of the number and percentage of subjects with [low, normal or high values] at each visit.

For categorical urinalysis data (absent/trace/positive and normal/abnormal) frequency tables, by treatment group, will be presented at each scheduled assessment. Shift tables from baseline to each post baseline visit will be presented for the number and percentage of subjects with [normal, abnormal].

For blood and urine sulfates, summary statistics (mean, median, SD, minimum and maximum) will be presented by treatment group at each scheduled assessment for actual values and changes from baseline. In addition, mean plots by visit and treatment group will also be provided. Finally, sulfates are supposed to be collected fasted, and since some assessments have been performed non-fasted, a sensitivity analysis will be made to describe actual values and changes from baseline by treatment group and fasting status at each scheduled assessment.

3.2.2.3 Vital signs

Vital signs (including body weight and temperature, systolic and diastolic BP and HR) will be listed at each assessment by treatment group and subject. Any unscheduled vital signs will be flagged [U] in the listing.

Baseline values will be defined as the last vital signs measurement collected prior to the first dose of study drug.

Summary statistics for weight, temperature, BP and HR will be presented at each scheduled assessment for actual values and changes from baseline by treatment group.

Additionally, a frequency table describing the variations at post-baseline visits will be provided with the following categories:

- Weight: < -2 kg, [-2; -1 kg[, [-1; 1 kg[, [1; 2 kg] > 2 kg.
- BP and HR: < -20 unit, [-20; -10 unit[, [-10; 10 unit[, [10-20 unit] and > 20 unit.

3.2.2.4 Tolerability

Tolerability will be collected using a Symptom Scale after each dose of treatment for stomach cramping, stomach bloating and nausea on a paediatric 5-point scale (with 1=no symptom, 2=mild, 3=bothersome, 4=distressing and 5=severely distressing symptoms).

Each symptom after each dose will be described by treatment group using a frequency table. Additionally, each symptom after each dose will be summarised by treatment group as well as the total score (sum of the three symptoms).

Finally, each symptom after each dose will be summarised by treatment group and use of nasogastric tube (Yes/No), as well as sex, age class and weight class.

3.2.2.5 Physical examination

A listing with the date of examination and the status of the examination (performed/not performed) will be provided by treatment group, subject and examination date.

3.2.2.6 Colonoscopy findings

Diagnosis or diagnostic findings made at colonoscopy will be reported as such and coded using SOC and PT. The colonoscopy findings, when reported, will then be described for incidence by SOC and PT by treatment group.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

No missing value will be replaced, except for the primary analysis where the missing preparation evaluations (because of colonoscopy not done because of inadequate preparation or preparation-related AEs) will be considered as failures.

In the description of qualitative parameters, subjects with a value counted as "missing" at a visit will be identified as subjects being not assessed.

If a value required a retest, the last reliable non-missing value will be taken into account if measured before the first intake of treatment; and the first non-missing reliable value for post-baseline assessments. An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of plausible values. Any retest or unscheduled assessments performed will be included in the individual subject data listings.

If there is a significant number of missing values for a subject (or if there is confirmed data appearing spurious), a decision will be made following consultation with the sponsor regarding the handling of these data in summaries, prior to database freeze.

Any repeat or additional assessments performed will be included in the individual subject data listings.

3.2.3.2 Missing or incomplete dates

In all listings, missing or incomplete dates should be left as they have been recorded. However, for calculation / sorting / assignation based on dates, the following methods will be used:

- The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).
- A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.
- If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (e.g. a medication with partial start and stop dates could be considered as prior and concomitant treatment).

Where this is possible, the derivations based on a partial date will be presented as superior inequalities (i.e. for an AE started in FEB2004 after the administration performed on 31JAN2004, the days since last dose will be "≥ 2", similarly the duration of ongoing AEs or medication will be "≥ xx" according to the start and last visit dates).

3.2.3.3 Outliers

A search of outliers should be performed before the database lock and actions with the sponsor should be defined.

3.2.4 Subject disposition

A listing of the randomisation numbers will be presented by treatment group and subject.

The number and percentage of subjects screened and included in each population will be presented by treatment group for the screened population and by country and centre. In addition, a flow chart will be provided with the number of subjects in each analysis population as well as colonoscopy performed and completed.

A listing of the inclusion and exclusion criteria will be provided by treatment group and subject, and subject eligibility will also be listed.

The reasons for subject exclusions from each population will also be tabulated by treatment group and overall on the randomised population.

A summary table will present the extent of subject exposure in the study for each treatment group by deriving the study duration defined as the number of days from the date of consent to the last study visit.

Listings of dates of assessments (relative day), of hospitalization entry and discharge and of study duration will be presented by treatment group and subject. The number and percentage of subjects at each planned visit during the study will be presented by treatment group and overall for the Safety population.

3.2.5 Withdrawals

Discontinued subjects will be listed and the numbers of subjects who were randomised, performed colonoscopy, discontinued and completed will be tabulated by treatment group and by country. Primary reasons for discontinuation of study treatment will be tabulated.

Number of subjects by visit will be provided by treatment as well as by country.

3.2.6 Demographic and baseline characteristics

The baseline is the last available assessment before administration of the IMP.

All demographic and baseline characteristics will be listed by treatment group and subject.

Summary statistics (n, mean, SD, median, minimum, maximum) or frequency counts will be provided for demographic and baseline characteristics (sex, country, age, age range ([12-14[/ [14-16[/ [16-18[), height, body weight, weight range (]40-50] /]50-60] / >60 kg) and BMI at baseline) by treatment group and overall for the ITT, mITT and PP populations if they differ by more than 10 %. Demographic and baseline characteristics will also be provided by country, age class weight class and sex on the ITT population.

Pubertal stage, if available, measured using Tanner stage for boys and girls will also be described at baseline using frequency counts by sex and overall, by treatment group and overall for the ITT population and mITT population if they differ by more than 10 %. The Tanner Grading Scale [7 & 8] based on a 5-point scale will be used to assess pubertal stage as follows:

Table 10 Tanner Grading Scale to assess the genital development in male subjects

Grade	Description	
Tanner I	Prepubertal: testes, scrotum, and penis of about same size and proportion as in early childhood.	Typically age ≤ 9 years.
Tanner II	Enlargement of scrotum and testes. Skin of scrotum reddens and changes in texture.	Typically age 9 to 11 years.
Tanner III	Enlargement of penis, at first mainly in length. Further growth of testes and scrotum.	Typically age 11 to 12.5 years.
Tanner IV	Increased size of penis with growth in breadth and development of glans. Testes and scrotum larger, scrotal skin darkened.	Typically age 12.5 to 14 years.
Tanner V	Genitalia adult in size and shape.	Typically age ≥ 14 years.

Table 11 Tanner Grading Scale to assess the pubic hair development in male subjects

Grade	Description	
Tanner I	Prepubertal: vellus over pubes is not further developed than over abdominal wall.	Typically age ≤ 10 years.
Tanner II	Sparse growth of long, slightly pigmented, downy hair, straight or slightly curled, chiefly at base of penis.	Typically age 10 to 11.5 years.
Tanner III	Considerably darker, coarser, and more curled hair. Hair spreads sparsely over junction of pubes.	Typically age 11.5 to 13 years.
Tanner IV	Hair now adult in type, but area covered is still considerably smaller than in adult. No spread to medial surface of thighs.	Typically age 13 to 15 years.
Tanner V	Spread up linea alba (male-type pattern)	Typically age ≥ 15 years.

Table 12 Tanner Grading Scale to assess the breast development in female subjects

Grade	Description	
Tanner I	No glandular tissue; areola follows the skin contours of the chest (prepubertal).	Typically age ≤ 10 years.
Tanner II	Breast bud forms, with small area of surrounding glandular tissue; areola begins to widen.	Typically age 10 to 11.5 years.
Tanner III	Breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast.	Typically age 11.5 to 13 years.
Tanner IV	Increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast.	Typically age 13 to 15 years.
Tanner V	Breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.	Typically age ≥ 15 years.

Table 13 Tanner Grading Scale to assess the pubic hair development in female subjects

Grade	Description	
Tanner I	Prepubertal: vellus over pubes is not further developed than over abdominal wall.	Typically age ≤ 10 years.
Tanner II	Sparse growth of long, slightly pigmented, downy hair, straight or slightly curled, chiefly along labia.	Typically age 10 to 11.5 years.
Tanner III	Considerably darker, coarser, and more curled hair. Hair spreads sparsely over junction of pubes.	Typically age 11.5 to 13 years.
Tanner IV	Hair now adult in type, but area covered is still considerably smaller than in adult. No spread to medial surface of thighs.	Typically age 13 to 15 years.
Tanner V	Adult in quantity and type with distribution of horizontal (or classically "feminine") pattern.	Typically age ≥ 15 years.

Moreover, the indication(s) for colonoscopy will also be described using frequency counts by treatment group and overall for the ITT population and mITT population if they differ by more than 10 %. Indications classified under category "Other" in the eCRF will be described as other and will be listed in a separate listing.

Additionally, haematology measured at baseline (including 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)) will also be described using summary statistics (n, mean, SD, median, minimum, maximum) after standardisation (see section 3.2.2.2 and reference 6) by treatment group and overall for the ITT population.

Moreover, a frequency table will be presented of the number and percentage of subjects with [low, normal or high values] at baseline.

Furthermore, female subjects of child-bearing potential have to perform a pregnancy test prior to baseline and the corresponding information will be listed when available.

3.2.7 Medical and surgical history

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 will be coded using MedDRA current version at Ipsen coding department at the time of database lock.

Listings will present the SOC, PT and reported term and will be sorted by treatment group, subject, chronological start date, SOC, PT and reported term.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by SOC and PT by treatment group and overall for the ITT population.

3.2.8 Subject compliance

A listing will be presented for drug administration for treatment preparation, residual volumes of preparation (volumes not taken by the subject) and start and stop times of intake by subject for each treatment group. In addition, information about the residual volume of water will be reported and listed for the Eziclen®/Izinova® treatment only.

Subject compliance to instructions of use is considered as a secondary endpoint and is described in section 3.2.1.2.10.

All major protocol deviations, defined prior to database freeze, will be listed by treatment group and subject. Additionally all major protocol deviations will be summarised on the ITT population and those with impact on the populations will also be described.

3.2.9 Prior and concomitant therapies

Medications will be coded using World Health Organization – Drug dictionary (WHO-DD) with the current version at Ipsen coding department at the time of database lock. The therapeutic class will correspond to the second level of Anatomic Therapeutic Class (ATC) code, which corresponds to the first 3 digits.

Non-drug therapies and surgical procedures will be coded using MedDRA Dictionary with the current version at Ipsen coding department at the time of database lock.

The date of first administration of study drug (study day 1) will be used as the cut-off date for the definition of prior and concomitant. A drug that started before study day 1 and is continuing at time of day 1 will be considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant will be flagged P, C and PC respectively, in all listings.

Prior and concomitant medications will be listed with the therapeutic class, preferred name and reported term and they will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and reported term.

Frequency tables of the number and percentage of subjects with at least one prior medication will be provided by therapeutic class and preferred name for the ITT population.

A similar table will be presented for concomitant medications.

Prior and concomitant non-drug therapies will be listed with the SOC, PT and reported term and they will be sorted by treatment group, subject, chronological start date, SOC, PT and reported term.

Concomitant surgical procedures will be listed with the SOC, PT and reported term and they will be sorted by treatment group, subject, chronological start date, SOC, PT and reported term.

3.2.10 Derived data

The derived data are data which are calculated according to Analysis Data Model (ADaM) standard from the raw data in the eCRF, not included in the Study Data Tabulation Model (SDTM) database, and displayed in the individual data listings. The list of derived data is displayed in Appendix 1.

3.2.11 Rules and data formats

Data will be presented using an appropriate number of decimal places (i.e. the number of decimal places used does not imply undue precision). Raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

For summary statistics, the following will be presented n, arithmetic mean, SD, median and the range (minimum, maximum).

Mean, SD and median values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported to 1 decimal place and 0 % will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population with available data. The denominator will be specified in a footnote to the tables for clarification if necessary.

All values below or above a limit of detection (e.g. < 0.1 or > 100) will be listed as such. For each parameter for which it is possible to have values below or above a limit of quantification, the rule to be used in the statistical tables is to replace values below or above a limit of quantification by the limit of quantification.

All text fields must be left justified and numeric or numeric with some text specification (e.g. not done, unknown, < 4.5, …) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

3.2.12 Pooling of centres

It is not planned to perform subgroup analyses on individual or groups of centres but efficacy analyses will be adjusted on countries.

3.2.13 Interim analysis

No interim analysis will be performed.

3.2.14 Role of expert safety data review committee

An Expert Committee will be appointed to review safety data. This Expert Committee will be chaired by the international coordinator and be composed of the coordinators from each country involved. Two reviews will be performed during data review meeting, first when 50 subjects will be included (i.e. when 20 % of the planned number of subjects have undergone colonoscopy corresponding to Visit 2 at Day 2) and second when 125 subjects will be included (when 50 % of the subjects have reached the Visit 2 at Day 2). Blinded descriptive tables will be produced by the study statistician on enrollment and disposition by country and overall, baseline characteristics (including age, sex, medical history, concomitant medications and indication for colonoscopy) safety with description of AEs (including overall summary of AEs and frequency tables by SOC and PT on SAEs, AEs, TEAEs, related TEAEs, AE leading to withdrawal and AE leading to death) and tolerability. Additionally, supporting individual blinded data listings on lab data, AEs, and tolerability will be provided.

3.2.15 Covariates and analysis of subgroups

Descriptive statistics for primary endpoint may be provided per country, age range ([12-14[/ [14-16[/ [16-18[years), weight range (]40-50] /]50-60] / >60 kg) and sex.

Exploratory analyses will be presented by repeating the primary analysis in the mITT by age class, weight class and sex using the main model with additional term for subgroup and the interaction treatment * subgroup, as well as the treatment * country interaction if found significant in the primary analysis, as follows:

```
proc logistic data=ADCC(where=(PARAM='Successful overall preparation' and
MITTFL='Y'));
    class TRTP(ref='KLEAN-PREP') COUNTRYC(ref='Largest country')
    SUBGROUP(ref='Class1') / param=glm;
    model AVALC(EVENT='Yes') = TRTP COUNTRYC /* TRTP*COUNTRYC
    */ SUBGROUP TRTP*SUBGROUP / link=logit lackfit firth;
    lsmeans TRTP*SUBGROUP / cl;
run;
```

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

The statistical analysis will be performed using a PC on a Windows 7 operating system.

4.2 Software

All tables, figures and listings (TFLs) will be produced and statistical analysis performed using SAS version 9.4 or higher [5]. All outputs will be in Microsoft Word Format.

4.3 Validation programs

Biotrial Biometrics will provide a validation plan to Ipsen identifying the methods of validation.

The study statistician is responsible for reviewing each output associated with the deliverable product. Program logs are checked by the statistical programmer for logical, syntax and fatal errors. The checks in SAS includes, but is not limited to, all ERRORS, WARNINGS, BY-VALUE merge messages, NOTES, and UNINITIALIZED variables. Program logs are also reviewed for accurate and consistent variable and observation counts following each procedure and data step.

The study statistician is responsible for checking and reviewing the work produced using double-programming for the primary endpoint and whatever method he/she feels is appropriate (e.g. SAS code review, hand calculation, etc.) to reassure of the quality of the output.

Outputs are reviewed for typographical errors, misspellings and nonsensical values or results and to check the consistency with the statistical analysis plan. Outputs are cross-checked against each other for accuracy and consistency. For statistical tables, listings, appendix listings, and figures, this procedure includes comparison of subject group numbers, counts of subjects at each observation point, and consistency of results for variables between outputs.

Findings of the quality control reviews are communicated to the party responsible for making necessary changes. The programs will be retested after modifications.

After final review, and when no further change is required to produce the deliverable, the statistical programmer and the study statistician have to complete and sign the quality control and statistical analysis results follow-up's validation checklist, to indicate that they have successfully performed all of their responsibilities. Copies of the internal QC forms produced for the validation process will be provided to the sponsor to support the validation.

4.4 Restitution of the programs

All programs (including macros and analysis datasets) producing the tables, listings and statistical outputs along with associated logs should be given to the sponsor when the TFLs and statistical analyses have been finalised.

5 CHANGES FROM PROTOCOL

It was planned in the protocol to tabulate the efficacy and safety (laboratory, vital signs and tolerability) results by treatment group and overall, but this is not relevant to pool them so only description by treatment group will be provided.

It was planned in the protocol to include the interaction treatment*country in the ANOVAs of the applicable secondary endpoints, but as for the primary analysis the interaction will rather be investigated and kept only if it is significant.

It was not planned in the protocol to perform secondary analyses on mITT and PP, but it was decided to take into account the significant difference in terms of number of patients between ITT and the mITT and PP populations in order to assess the robustness of the results.

It was not planned in the protocol to present the primary endpoint according to subgroups (age class, weight class and sex), but descriptive statics have been added to explore the primary results.

It was not planned in the protocol to describe the time between the last intake of fluids and the start of colonoscopy procedure, but as this factor has been shown to be a major contributor to quality in adult patients it has been decided to add this description (Hassan et al.).

It was planned in the protocol to exclude from the PP population all subjects with major deviations, but some major deviations do not have an impact on the analyses, so they have been identified in the Protocol Deviation Document and the definition of the PP population has been updated to only consider the deviations having an impact on the analyses.

6 REFERENCES

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

2 Lai EJ, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston Bowel Preparation Scale: A valid and reliable instrument for colonoscopy-oriented research. Gastrointest Endosc. 2009;69(32):620–625.

3 International Conference on Harmonisation (ICH) E9 and Federal register Vol. 63, No. 179 (September 1998).

4 SAS, Version 9.3. SAS Institute Inc., Cary, NC, USA, 2012.

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7 Marshall WA, Tanner JM (February 1970). "Variations in the pattern of pubertal changes in boys". Arch. Dis. Child. 45 (239): 13–23.

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7 APPENDICES

Appendix 1 Derived data

The following derived data will be calculated:

(1) Treatment group

Treatment groups will be defined as “Eziclen/Izinova” and “Klean-Prep”.

(2) Study duration

Study duration (days) will be calculated as (last visit attended - date of informed consent) + 1.

(3) Successful treatment preparation

- A successful preparation will be derived from a colon cleansing scored as excellent (4) or good (3).
- A failure preparation will be defined as:
  - Fair (2) or poor (1) according to colon cleansing score,
  - 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.

(4) Time to clear effluent

It is defined as the time (expressed in hours) from the first intake of prescription to the first clear watery stool occurrence if any, or to the time of colonoscope introduction, if no clear watery stool is observed before the beginning of the procedure and then the time will be considered as censored for the survival analysis. See section 3.2.1.2.3.

(5) Completion of the procedure

"Yes" if the colonoscopy reached the caecum and the item "Was physician able to reach the caecum?" is "Yes", "No" otherwise.

(6) Duration of the intubation

It is defined as the time (expressed in minutes) from colonoscope introduction to caecal intubation.

(7) Duration of the examination

It is defined as the time (expressed in minutes) from caecal intubation to colonoscope withdrawal.

(8) Need of a rescue treatment

"Yes" if a rescue medication was administered and the item "Was any enema needed to achieve preparation?" is "Yes", "No" otherwise.

(9) Need of a nasogastric tube to complete preparation

"Yes" if a nasogastric tube was inserted and the item "Was a nasogastric tube inserted?" is "Yes" at dose 1 or dose 2, "No" otherwise.

(10) Compliance in percentage

The percentage of compliance is defined as (planned volume - residual volume) / planned volume, adding up the solution and water volume where applicable.

The planned volume is 750 mL for Eziclen (375 mL per dose), 1500 mL for hydration (750 mL per dose) and 70 mL/kg for Klean-Prep® with a maximum of 4000 mL (maximum 2000 mL per dose).

(11) Compliance with the instructions of use

A subject is considered as compliant with the instructions of use if he/she drinks the whole preparation (100 % of compliance) and any required further fluid intake (100 % of compliance).

The planned volume is 750 mL for Eziclen (375 mL per dose), 1500 mL for hydration (750 mL per dose) and 70 mL/kg for Klean-Prep® with a maximum of 4000 mL (maximum 2000 mL per dose).

(12) Compliance in class

The compliance in class is defined from the compliance in percentage as follows:

- 100 %,
-]100-75],
-]75-50],
- < 50 %.

(13) Lesions caused by colonic lavage

Histological examination results of lesions caused by colonic lavage will be identified among the adverse events by looking for the term "colonic lavage" in the verbatim term, since the investigator should identified the suspected lesions using "suspected to have been caused by colonic lavage". The occurrence (Yes/no) will then be derived for each subject.

(14) Baseline

Baseline will be derived as the last available assessment before administration of the IMP.

(15) Changes from baseline

Changes from baseline will be calculated as a difference from baseline (e.g. assessment at the visit – assessment at baseline).

(16) Therapeutic Class.

The therapeutic class will correspond to the first 3 digits of the ATC code. The decoding of the therapeutic class will be done from the WHO-DD (current version at the time of database lock).

(17) Prior and concomitant flags

The date of first administration of study treatment (study day 1) is used as the cut-off date for the definition of prior and concomitant medications. A drug started before study day 1 and continuing at time of Day 1 is considered as both, prior and concomitant. Prior, concomitant and both prior and concomitant will be coded as P, C and PC respectively.

(18) Concomitant therapy duration

If times are available, the duration of concomitant treatments will be calculated as (end date/time - start date/time). If at least one time is missing, the duration of concomitant treatments will be calculated as (end date - start date) + 1. If the recorded end date is continuing at the end of the study then the end date will be listed as “ongoing” and the duration will be approximated as “≥(last attended visit date – start date) + 1” day(s). If the start date or the end date are partial, the duration will be presented as an inequality “≥xx” day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004

and end date=01FEB2004] but if both are partial or one is missing the duration will not be presented.

(19) Adverse event duration

If the start and end dates of the adverse event are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration will be calculated as (end date/time – start date/time) and presented in days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (end date - start date) + 1 and presented in days. If the recorded end date is continuing at the end of the study, the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date) + 1" day(s). If the start date or the end date are partial the duration will be presented as a superior inequality "≥xx" day(s) [i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004].

Appendix 2 Data presentation and tables, figures and listings' templates

Data listings are presented for all screened subjects.

Footnotes should be used to clarify ambiguities (e.g. the denominator used to calculate a percentage or notes for the programmer). If the number of footnotes is high, they could be presented only in the last page, with on each page the following footnote “See last page for listing notes”. The order of the footnotes for key symbols (*, ~) will be in the order that they appear in the listing.

The title of each generated TFL should appear bookmarked within Word (one single bookmark per TFL) to allow document publishing by Ipsen.

TFLs templates are provided in a separate document CCI [redacted]

The TFLs will be presented in landscape, in a fixed font (Courier New) with a minimum size 8 and according to the standard margins defined in procedure CCI [redacted].

The page number of each TFL shell (n of N) represent n=page number of the listing and N=total number of pages for that specific TFL.

Each TFL must be presented in an independent, separate Word file for each ICH heading (e.g. Listings 16.2.9.X combined in one file).

A statistical appendix for inclusion in the study report will be provided.

All the SAS outputs produced during the statistical analyses will be included without reworking the data (raw output).

For the logistic regression, the output of the LOGISTIC procedure within SAS will be presented. The results of the model checking procedures done through the robustness analyses will also be included.

For the ANOVA, the output of the MIXED procedure within SAS will be presented. This will include the overall ANOVA table, parameter estimates, least square means for the treatment group with 95% CIs and the associated p-values.

For the CMH analyses, the output of the FREQ procedure within SAS will be presented. This will include the frequency table and CMH statistics.

This output should contain the study number, the date, the number of pages printed by SAS and the table number to which it refers. Any other relevant information will be added in the statistical appendix.

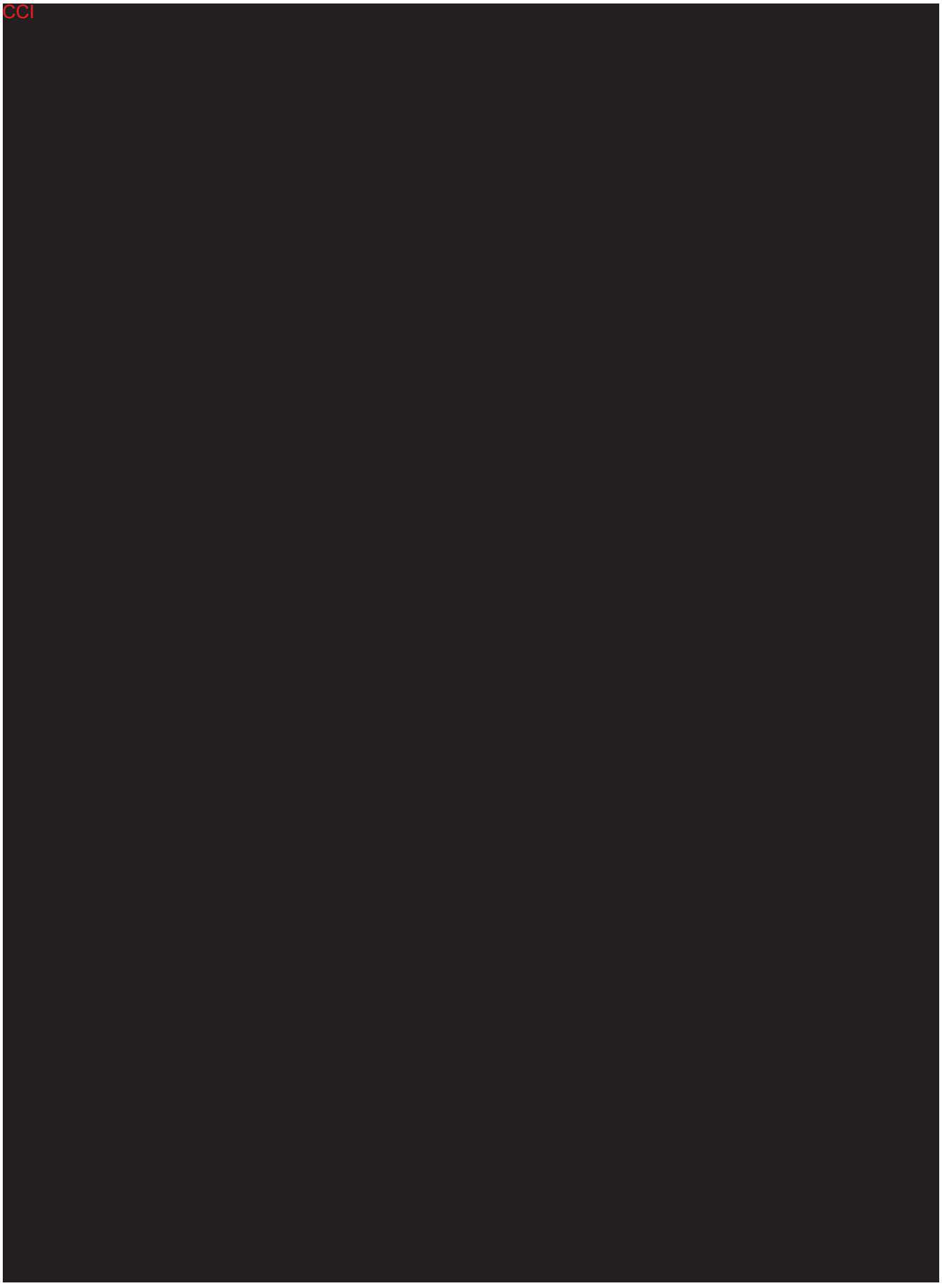
Appendix 3 List of tables, figures and listings

CCI

CCI

CCI

[redacted]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[redacted]

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[redacted]

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