# PROTOCOL TITLE: EFFICACY OF DIOSMECTITE (SMECTA®) IN THE SYMPTOMATIC TREATMENT OF ACUTE DIARRHOEA IN ADULTS. A MULTICENTRE, RANDOMISED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL GROUPS STUDY

STUDY PROTOCOL

STUDY number: F-FR-00250-105

(Diosmectite- BN 00250)
EudraCT number: n° 2015-001138-10

Final Version (with Amendment No. 4): 07 January 2019

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

**Study Sponsor:**
Ipsen Pharma SAS
65 quai Georges Gorse
92100 Boulogne-Billancourt, France
Tel: PPD
Fax: PPD

**Monitoring Office: and/or CRO**
PPD
PPD
Ipsen Pharma SAS
65 quai Georges Gorse
92100 Boulogne-Billancourt, France
Tel: PPD
Fax: PPD

**Co-ordinating Investigator:**
PPD
Délégation à la Recherche
Centre Hospitalier Régional Universitaire de Lille
2, avenue Oscar Lambret,
59037 Lille, France Cedex
Tel: PPD
Fax: PPD

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

## INVESTIGATOR'S AGREEMENT

**Investigator Agreement and Signature:**
I have read and agree to Protocol F-FR-00250-105 entitled Efficacy of the diosmectite (Smecta®) in the symptomatic treatment of acute diarrhoea in adults. A multicentre, randomised, double blind, placebo-controlled, parallel groups study. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: [ ]
TITLE: INVESTIGATOR SIGNATURE:

DATE:
OFFICE: [ ]
[ ]
[ ]
[ ]
[ ]

**Sponsor's Representative Signature:**
NAME: PPD

TITLE: PPD

SIGNATURE:

DATE:
OFFICE: Ipsen Pharma SAS
Medical Department
65 quai Georges Gorse
92100 Boulogne-Billancourt, France
Tel: PPD
Fax: PPD

## COORDINATING INVESTIGATOR'S AGREEMENT

**Coordinating Investigator Agreement and Signature:**
I have read and agree to Protocol F-FR-00250-105 entitled Efficacy of the diosmectite (Smecta®) in the symptomatic treatment of acute diarrhoea in adults. A multicentre, randomised, double blind, placebo-controlled, parallel groups study. I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: PPD
TITLE: COORDINATING INVESTIGATOR SIGNATURE:

DATE:
OFFICE: Délégation à la Recherche
Centre Hospitalier Régional Universitaire de Lille
2, avenue Oscar Lambret
59037 Lille
France Cedex

## SUMMARY OF CHANGES

The current version of the protocol was released on 07 January 2019 and includes Amendment 4. The corresponding amendment form was prepared and is provided in Appendix 6 (Table 1).

**Table 1 List of Protocol Amendments**

| Amendment | Release date | Amendment form |
|---|---|---|
| 1 | 25 January 2016 | Appendix 4 |
| 2 | 10 March 2016 | Appendix 5 |
| 3 | 08 August 2017 | Appendix 6 |
| 4 | 07 January 2019 | Appendix 7 |

## SYNOPSIS

**NAME OF SPONSOR/COMPANY: IPSEN PHARMA SAS**

**Name of finished product**: SMECTA®

**Name of active ingredient(s)**: Diosmectite- BN 00250

**Title of study**: **EFFICACY OF DIOSMECTITE (SMECTA®) IN THE SYMPTOMATIC TREATMENT OF ACUTE DIARRHOEA IN ADULTS.**

**A MULTICENTRE, RANDOMISED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL GROUPS STUDY.**

**Study number**: F-FR-00250-105

**Number of planned centres**: 90 centres in 6 countries, including Algeria, Czech Republic, Poland, Tunisia, Lebanon and Egypt.

| **Planned study period**: | **Phase of development**: |
|---|---|
| December 2015 to September 2019 | Phase IV |

**Objectives**:

**Primary**:

- To demonstrate that diosmectite efficacy is superior to placebo regarding time to recovery of an acute diarrhoea episode presumed of infectious origin in adult subjects.

**Secondary**:

- To demonstrate that diosmectite efficacy is superior to placebo regarding other efficacy criteria.
- To assess the clinical tolerance of diosmectite versus placebo.

**Methodology**:

The study is a multicentre, prospective, double blind, placebo-controlled randomised comparative study. Efficacy and safety of diosmectite (administered at a dose and treatment regimen in line with the Diosmectite Beaufour Summary of Product Characteristics (SmPC) approved in France (the daily dosage can be doubled at the beginning of treatment for acute episode), i.e. 2 sachets containing 3 g of diosmectite each, three times a day (TID), a minimum of 24 sachets to be taken in 4 or 5 days and with a maximum of 48 sachets to be taken in 8 or 9 days) will be evaluated in adult subjects with a recent episode of acute diarrhoea presumed of infectious origin.

**Therapeutic schema**:

Two sachets (TID): 6 sachets per day (active or placebo):

- From Day 1 to Day 4 or Day 5:
  - Mandatory treatment period = 24 sachets.
- From Day 5 to Day 8 or Day 9:
  - If one formed stool is followed by a nonwatery stool, i.e. recovery, the treatment is stopped.
  - In any case, treatment stops after a maximum of 48 sachets have been taken

At Visit 1, subjects will be blindly randomised to one of the two treatment groups (either active or placebo according to the randomisation list). Each randomised subject will receive a treatment box containing 48 sachets.

The treatment can be stopped after 4 days in case of 1 formed stool followed by a nonwatery stool. At Visit 2 (Day 5 or Day 6), a physical examination will be performed and safety will be assessed.

In case the subject has not recovered from diarrhoea at Visit 2, he/she will prolong the treatment with a maximum of 48 sachets up to Day 8 or Day 9 at the latest. For these subjects only, a third visit (Visit 3; Day 9 or Day 10) is planned.

**Number of subjects planned**:

A total of 726 assessable subjects are planned to be included in the study.

As it is assumed 5% subjects withdrawn without recovery and a maximum of 10% nonevaluable subjects, 854 subjects (427 per treatment group) will have to be randomised in order to achieve an 80% power.

**Diagnosis and criteria for inclusion**:

**Inclusion criteria:**

(1) Provision of written informed consent prior to any study related procedures,

(2) male or female subject (outpatient) legally considered as an adult (age of majority). In Czech Republic the upper limit of age will be 70 years inclusive.

(3) subject has a diagnosis of acute diarrhoea presumed of infectious origin, defined as:
- the passage of 3 or more unformed loose or watery stools (rated according to the Bristol scale) per day without associated alarm symptoms*
- having started within 48 hours before Visit 1 (first study drug intake time).

(4) subject has, usually, normal bowel habits (Rome III criteria)** , i.e. at least 3 stools per week and no more than 3 stools per day,

(5) subject must be willing and able to comply with study restrictions and willing to return to the clinic for the follow up evaluation(s) as specified in the protocol.

*Symptoms considered as alarm symptoms are identified in the exclusion criteria (1)

** Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional Bowel Disorders. Gastroenterology 2006;131:1480–91.

**Exclusion criteria:**

**Exclusion criteria related to acute diarrhoea episode:**

(1) At least one of the following alarm symptoms*
- Bloody diarrhoea*,
- pus in the stools*,
- fever ≥38.0°C*,

- moderate or severe dehydration according to World Health Organisation (WHO) definition, requiring intravenous (IV) rehydration*,
- repeated vomiting*,
- persistent abdominal pain*

*These symptoms are considered as alarm symptoms

(2) other episode of acute watery diarrhoea within the previous 30 days,

(3) persistent diarrhoea, defined as acutely starting episode of diarrhoea lasting more than 14 days,

(4) history of chronic diarrhoea (Rome III criteria); i.e. 3 or more loose or watery stools per day for at least 12 weeks, consecutive or not, in the preceding 12 months,

(5) traveller's diarrhoea defined as a diarrhoeal episode due to contamination experienced by subjects having travelled in at risk countries, or coming from abroad and experiencing locally an acute diarrhoea episode, occurring usually within the first 2 weeks of the stay in a foreign environment.

**Exclusion criteria related to drugs:**

(6) Diarrhoea suspected to be induced by drug, for example:
- antibiotic therapy, including Clostridium difficile-induced diarrhoea, within 1 week before entry in the study,
- laxative agent,
- thyroid hormone (at a nonstabilised dosing),
- colchicine intake, etc…

(7) anti-diarrhoeal agent intake during the last month,

(8) any subject requiring repeated intake of a drug with a narrow therapeutic margin (for example, digoxin, theophylline, etc…),

(9) history of hypersensitivity to diosmectite or its excipients or placebo components,

(10) subject likely to require treatment during the study with drugs that are not permitted by the study protocol (for example, antibiotic agent, anti-diarrhoeal agent, antiemetic drug, antispasmodic drug),

(11) use of any investigational medication within the last 30 days before entering this study,

(12) subject who previously entered in a clinical study within the past 30 days.

**Other Digestive Exclusion criteria:**

(13) History of gastric or intestinal resection, vagotomy,

(14) known digestive malabsorption disease, including coeliac disease

(15) known lactose intolerance,

(16) any suspicion of abdominal surgery need,

(17) known inflammatory bowel disease.

**Other Exclusion criteria:**

(18) Known Human immunodeficiency virus (HIV) positive status,

(19) known or suspected immunosuppression,
(20) known severe renal or hepatic insufficiency,
(21) Uncontrolled diabetes of all types and non insulin dependant diabetes during first 6 months of medical treatment and other known endocrine disease,
(22) history of, or known current, problems with alcohol abuse and/or known drug addiction (cocaine, heroin, hashish…),
(23) previous enrolment in this study,
(24) any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
(25) Pregnant or lactating women

Test product, dose, mode of administration:

The test product consists of sachet of powder for suspension for oral use containing 3 g of diosmectite.

Diosmectite will be presented in sachets according to the following composition:

- active substance:
  - diosmectite: 3 g
- other components:
  - vanillin, saccharin sodium and glucose monohydrate.

Each sachet will be mixed with water prior to administration

The regimen below will be 2 sachets TID:

- 2 sachets in the morning,
- 2 sachets at mid-day,
- 2 sachets in the evening.

**Duration of treatment:**

This study will consist of an inclusion visit, i.e. Visit 1 (the subject will be randomised and start treatment that day) and a 4- to 9-day day dosing period. Subjects are expected to take the study treatment in this study with a minimum of 24 sachets to be taken in 4 days or 5 days and with a maximum of 48 sachets to be taken in 8 or 9 days. Visit 2 will be on Day 5 or Day 6 and Visit 3 will be on Day 9 or Day 10.

The subject's participation in the study will be considered to have ended when the subject will have recovered from diarrhoea, defined as one formed stool followed by a nonwatery stool and when the last follow-up visit is performed.

The overall duration of the study for each subject will be 5 to 6 days (if subject has recovered by Visit 2) or 9 to 10 days (duration of study treatment can be from 4 to 9 days).

**Reference therapy, dose and mode of administration**:

**Placebo**:

Placebo will be presented in sachets according to the following composition:

- titan dioxide, Spray dried liquid glucose, vanillin, saccharin sodium, glucose monohydrate,

- caramel colouring E 150 B.

The regimen will be the same as for the active treatment.

**Criteria for evaluation**:

**Efficacy:**

Primary endpoint and evaluation: time to recovery, defined as the time (hours, minutes) from the 1st study treatment intake to the first formed stool (this formed stool must have been followed by a nonwatery stool). Consistency will be rated according to the Bristol scale.

Secondary endpoints and evaluations:

(a) abdominal pain intensity (rated with a 5-point ordinal scale: 0 = absent, 1= mild, 2 =moderate, 3 = severe, 4= very severe) per 12-hour period,
(b) time (hours, minutes) from diarrhoea onset to recovery defined as first formed stool followed by a nonwatery stool
(c) time (hours, minutes) from first watery stool to the first formed stool
(d) time (hours, minutes) from the 1st study treatment intake to the last watery stool,
(e) number of stools, per 12-hour period,
(f) number of watery stools, per 12-hour period,
(g) Percentage of subjects with associated symptoms such as nausea, vomiting, abdominal pain and anal irritation, per 12-hour period.

**Safety:**

Occurrence of adverse events (AEs) reported by the subject from the time that the subject gives informed consent until 7 days after the end of the study treatment. Vital signs (blood pressure, heart rate in sitting position, respiratory rate, body temperature and body weight) measurement at each visit, physical examination findings and measurements, at each visit, body height (at Visit 1 only), concomitant medication usage throughout the study.

**Microbiological Tests:**

A fresh stool will be collected as soon as possible after inclusion for microbiological laboratory testing (for virology, bacteriology and parasitology testing) in order to determine the microbiological status of this acute diarrhoea episode , i.e. the absence/presence of the following faecal pathogens:

<u>Virology testing</u>

- rotavirus,
- adenovirus,
- norovirus,

<u>Bacteriology and parasitology testing</u>

- enteropathogenic and enterotoxigenic Escherichia coli (E. coli),
- staphylococcus aureus,

- shigella,
- salmonella,
- campylobacter,
- yersinia enterocolitica,
- amoeibiasis (entamoeba histolytica),
- giardia/lamblia.

**Statistical Methods**:

**Sample size rationale:**

Assuming a median time to recovery of 55 hours in the active group and 70 hours in the placebo group (corresponding to a difference of 15 hours as evidenced in the Khediri et al study [Gastroenterology Research and Practice, Volume 2011, Article ID 783196, http://dx.doi.org/10.1155/2011/783196]), 363 subjects per treatment group (726 in total) will be required in order to detect such a difference using a two-sided Gehan-Wilcoxon test at a significance level of 5% and a power of 80%.
It is assumed a maximum of 5% of subjects prematurely withdrawn without recovery and a maximum of 10% of nonevaluable subjects (because of poor/incomplete diary completion).
Accordingly, 854 subjects (427 per treatment group) will be required in order to achieve an 80% power.

**Planned Statistical analyses:**

**Populations:**

Following study populations will be defined:

- Intent to treat (ITT) population: all randomised subjects analysed according to the arm to which they were randomised.
- Safety population: all randomised subjects with at least one dose of study medication analysed according to the actual treatment received.
- Modified Intent to treat (mITT) population: all randomised subjects who received at least one dose of study medication and have at least one efficacy assessment for the primary endpoint***. Subjects will be analysed according to the arm to which they were randomised.
- Per protocol (PP) population: all subjects in the mITT population for whom no major protocol violations/deviations occurred.

***The efficacy assessment will be based on the Diary evaluation booklet (DEB), therefore subjects who have not filled in the DEB will be excluded from the efficacy analysis.

All efficacy endpoints and subject demographics will be evaluated in the ITT population.
Treatment administration/compliance and safety will be analysed in the Safety population.
Supportive analysis using mITT and PP population will be carried out.

Primary endpoint:

The primary endpoint (time from the 1st treatment dose intake ($T_0$) to recovery defined as first formed stool followed by a nonwatery stool, in hours) will be analysed using a time to event analysis (Kaplan-Meyer method) and the comparison between the two treatment groups will be done using Gehan-Wilcoxon test, as the efficacy of the active product is

expected quickly after study intake. In this analysis, subjects prematurely withdrawn or ending the study without recovery will be censored.

Estimated medians and quartiles will be provided with their 95% confidence intervals (CIs), leading to a comparison of the time between groups where 25, 50 and 75% of the subjects have recovered.

Descriptive statistics for efficacy evaluation may be provided by country, season, absence/presence of faecal pathogens.

Secondary endpoints:

The secondary endpoints related to time to event (efficacy variables b, c and d) will be analysed using the same methodology as for the primary efficacy endpoint.

Regarding the secondary endpoints based on number of stools per 12-hour period, a repeated measurement model of number of stools during the post baseline period will be fitted using the analysis of covariance (ANCOVA) method if data warrant. The model will include as fixed effects number of stools 24 hours before randomisation (baseline), treatment, time point (12-hour period) and the treatment by time point interaction effect. The same analysis will be performed for number of watery stools.

Regarding the efficacy endpoints related to binary data, a general linear mixed model will be fitted if data warrant in order to evaluate the treatment effect at each 12-hour period, according to the same methodology as described above.

Safety endpoints:

AEs per treatment group will be described for the Safety population.

AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and AE listings will be presented by subject, system organ class and preferred term.

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

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

Summary statistics (mean, median, SD and range as appropriate) by treatment group and overall will be presented for vital signs (blood pressure, heart rate in sitting position, respiratory rate, body temperature, body weight), at each assessment with change from baseline.

# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| ABBREVIATION | Wording Definition |
|---|---|
| **AE** | Adverse event |
| **ANCOVA** | Analysis of covariance |
| **ATC** | Anatomical Therapeutic Chemical (ATC) |
| **CA** | Competent Authorities |
| **CFR** | Code of Federal Regulations (United States of America) |
| **CI** | Confidence interval |
| **CRO** | Contract research organisation |
| **CSR** | Clinical study report |
| **DEB** | Diary evaluation booklet |
| **EDC** | Electronic data capture |
| **eCRF** | Electronic case report form |
| **ESPGHAN** | European Society for Paediatric Gastroenterology, Hepatology and Nutrition |
| **ESPID** | European Society for Paediatric Infectious Diseases |
| **FDA** | Food and Drug Administration |
| **GCP** | Good Clinical Practice |
| **IB** | Investigator's Brochure |
| **ICH** | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IEC** | Independent ethics committee |
| **IMP** | Investigational Medicinal Product |
| **IRB** | Institutional review board |
| **ITT** | Intent to treat |
| **IV** | Intravenous |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **mITT** | Modified Intent to treat |
| **ORS** | Oral rehydration salts |
| **PI** | Package Insert |
| **PP** | Per protocol |
| **PDD** | Protocol deviation document |

| | |
|---|---|
| **SAE** | Serious adverse event |
| **SAP** | Statistical analysis plan |
| **SAS®** | Statistical Analysis System® |
| **SD** | Standard deviation |
| **SmPC** | Summary of Product Characteristics |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TEAE** | Treatment emergent adverse event |
| **TFL** | Tables, figures and listings |
| **TID** | Three times a day |
| **TMF** | Trial master file |
| **US** | United States |
| **WHO** | World Health Organization |
| **UNICEF** | United Nations Children's fund |

# 1 BACKGROUND INFORMATION

## 1.1 Introduction

Diarrhoea is one of the most frequent conditions around the world. Its acute form is among the leading causes of morbidity and mortality in developing countries accounting for 5 to 8 million deaths per year in infants and children [1]. In Western countries, acute diarrhoea is not a life-threatening disease but is one of the most common diagnoses in general practice. The annual rate of diarrhoea illness among adults in Western Europe and the United States (US) averages about one episode per person per year [1, 2, 3]. The affection is usually self-limited but symptoms can be disturbing and incapacitating. It is commonly recognised that its symptoms lead to substantial costs for the society as it is estimated that half of the episodes are related to missed workdays [4]. Diarrhoea may be acute or chronic, and appropriate therapy depends on proper diagnosis. Prevention and treatment of dehydration is the cornerstone of patient management for acute diarrhoea, particularly in young children and the elderly. However, reducing diarrhoea duration and relief of associated symptoms (abdominal pain, cramps from intermittent spasm, distension from gas produced by fermentation, discomfort due to the number of bowel movements and associated irritation of the perianal region) are also important treatment goals.

The recommended therapeutic regimen is to provide oral rehydration solutions (ORS) and to continue food intake. Although ORS effectively mitigates dehydration, it has no effect on the duration, severity, or frequency of diarrhoeal episodes. Adjuvant therapy with micronutrients, probiotics, or anti-diarrhoeal agents may thus be useful [5]. Diosmectite has demonstrated efficacy in the treatment of acute watery diarrhoea in children. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Paediatric Infectious Diseases (ESPID) treatment guidelines consider the use of racecadotril, diosmectite, or probiotics as possible adjunctive therapy to ORS. Only racecadotril and diosmectite reduce stool output, but no treatment has yet been shown to reduce hospitalisation rate or mortality. Appropriate management with validated treatments may help reduce the health and economic burden of acute diarrhoea in children worldwide [5], and acute gastroenteritis is best managed using a few simple, well-defined medical interventions [6].

Currently, there is no international consensus for the treatment of acute diarrhoea in adults as opposed to children where treatment with diosmectite or racecadotril is recommended (ESPGHAN and ESPID treatment guidelines).

A total of six randomised comparative studies have evaluated the efficacy of diosmectite in the treatment of acute diarrhoea in adults. The clinical development programme of diosmectite for the symptomatic treatment of diarrhoea has taken place over 2 periods. In the early period (up to 2000), the number of patients enrolled was usually small and the methodological quality limited.

In the later period (since 2000), one study initiated by Ipsen [7], has been conducted in accordance with contemporary clinical trial methodology and guidelines for the assessment of anti-diarrhoeal agents and conformed to a rigorous randomised, placebo-controlled, blinded design. This study, considered as pivotal, performed in Tunisia in 2005-2006, was a placebo-controlled study in 346 patients using time to recovery from diarrhoea as the primary outcome measure. This study showed a

significant benefit of diosmectite versus placebo which was of clinical relevance. However, the study conducted in Tunisia is the only placebo-controlled study that has been conducted for the indication of acute diarrhoea in adults. CCI [redacted]

## 1.2 Name and Description of Investigational Medicinal Product

The investigational medicinal product (IMP) is the Diosmectite BEAUFOUR product approved in France, which differs only from SMECTA®, a diosmectite marketed in more than 73 countries, by the aroma (respectively vanilla versus orange and vanilla) known by the main product trade name SMECTA® (French approved name) and licenced in more than 73 countries. The investigational medicinal product is further referred to in this protocol as diosmectite. References to SMECTA® are made in this protocol as Diosmectite BEAUFOUR and SMECTA® are considered as similar products. Diosmectite is also known as intergrade smectite of beidellitic nature or beidellitic montmorillonite. Diosmectite is a gastrointestinal adsorbent mucostabiliser according to the Anatomical Therapeutic Chemical (ATC) classification index form. The active substance of diosmectite is dioctahedral smectite, a naturally-occurring double silicate of aluminium and magnesium belonging to the group of dioctahedral smectites.

Diosmectite is composed of units made of two silica tetrahedral sheets encompassing a central alumina octahedral one. Iron, magnesium and calcium may replace aluminium in the alumina octahedral layer, originating negative charges inside the sheets. The ionic deficiency is balanced by exchangeable cations between the layers [8]. According to the lamellar structure and the ionic properties, diosmectite exhibits a high adsorption to the gastrointestinal mucus. Diosmectite binds in a noncovalent manner with the mucosal glycoproteins and increases the rheological properties of the mucus. As a consequence, the mucus provides a stable layer over the luminal surface, reinforcing the mucus barrier to chemical agents and micro-organisms [9].

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

## 1.3 Findings from Nonclinical and Clinical Studies

Diosmectite and mineral clays with adsorptive properties have been extensively used orally in human medicine. Silicate clays are also used as a bulking or opacifying agent, absorbent, emulsion stabiliser, viscosity increasing agent and colorant in many cosmetic or noncosmetic products [10].

Given the mineral nature, the size of the structure and the close adherence to the mucus gel, absorption through the gastrointestinal tract is not expected. Primary pharmacodynamic studies were conducted to investigate the local mode of action of diosmectite. The objectives of these studies were to characterise the binding of diosmectite to mucosal glycoproteins and the protector effect on gastrointestinal cells.

The toxicological profile has been established during the development of diosmectite. Oral administration was used in nonclinical studies since it is the intended route for clinical administration. Acute studies were conducted in rats and mice and repeated dose studies were conducted in rats and dogs. In vivo genotoxicity studies were conducted in rats and mice.

Further details may be found in the current investigator's brochure (IB).

## 1.4 Known and Potential Risks and Benefits to Human Subjects

Data on the safety of diosmectite have been collected from clinical studies involving over 3000 subjects and from over 30 years of postmarketing experience. Diosmectite appears to be well tolerated and the absence of any obvious systemic treatment related side effects can be explained by the fact that systemic exposure to this medication is negligible. The most frequently described side effect of diosmectite is constipation, which is usually of mild to moderate severity and transient. However, cases of severe constipation and aggravation of pre-existing constipation have been reported very infrequently from spontaneous reporting. Hypersensitivity reactions have also been documented in subjects treated with diosmectite through spontaneous reporting. Both constipation and hypersensitivity reactions are listed events for diosmectite.

The benefits of diosmectite in the treatment of acute diarrhoea in adults have been demonstrated in a large placebo-controlled randomised clinical trial [7]. In this study, the median duration of diarrhoea was reduced by 15 hours in subjects treated with diosmectite compared with the placebo group. A reduction in the duration of diarrhoea of 15 hours (22%), allowing a more rapid return to normal activity was considered as highly clinically relevant. The amplitude of the treatment effect was comparable to that previously reported with loperamide, a reference anti-diarrhoeal medication, and direct comparative trials have not demonstrated any inferiority of diosmectite with respect to loperamide. With regard to improvement in associated symptoms, another relevant benefit in this indication, the placebo-controlled study did not demonstrate a significant treatment effect, although it was not designed or necessarily powered for this variable.

With respect to risk for the subjects, the safety profile of diosmectite is acceptable in the target indications. At last an acute diarrhoea episode in adults without concomitant alarm symptoms, according to the selection criteria, is usually self-resolving and not life-threatening. All subjects should receive recommended hydration and diet advice according to WHO guidelines [11].

The benefit to risk ratio for diosmectite in the treatment of acute diarrhoea in adults can thus be considered favourable for the recruited subjects, therefore the potential uncertainties and risks for the subjects included in this new study should be very low.

CCI [redacted] The sample size calculation was based upon the assumption that the duration of the diarrhoea episode would be shorter than 8 days for the majority of the subjects (it was planned 7 days in the previous study) with few expected late censures. The definition of recovery (i.e. one formed stool followed by a nonwatery stool); was selected to guarantee the clinical relevance of the primary criterion as it was confirmed by the evaluation of the results of the Tunisian study by expert clinical gastroenterologists and from Health Authorities. However, this is much more constraining compared to trials performed in the early period up to 2000, which defined recovery as the first nonliquid stool.

Additional information regarding risks and benefits to human subjects may be found in the IB.

## 1.5 Selection of Investigational Medicinal Products and Dosages

In this multicentre, prospective, double blind, placebo-controlled randomised comparative study, diosmectite or placebo will be administered at a dosing of 2 sachets three times a day (TID) with a minimum of 24 sachets to be taken in 4 or 5 days and with a maximum of 48 sachets to be taken in 8 or 9 days in adult subjects with a recent episode of acute diarrhoea presumed of infectious origin. The dose and treatment regimen are in line with diosmectite Summary of Product Characteristics (SmPC) (the daily dosage can be doubled at the beginning of treatment for acute episode), rehydration, and special diet. The mandatory amount of sachets to be taken is 24 sachets within 4 or 5 days, then up to recovery (one formed stool, followed by a nonwatery stool). The treatment will be stopped after 8 or 9 days treatment at the latest.

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

## 1.6 Compliance Statement

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

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

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

## 1.7 Population to Be Studied

The study will enrol subjects (outpatients) legally considered as adults (age of majority) with a recent episode of acute diarrhoea presumed of infectious origin, defined as the passage of 3 or more unformed (loose or watery) stools per day within the first 48 hours.

# 2 PURPOSE OF THE STUDY AND STUDY OBJECTIVES

## 2.1 Purpose of the Study

Oral Rehydration Salts are not routinely needed in healthy adults suffering from acute diarrhoea, although rehydration through increased intake of normal beverages is recommended. No specific recommendations for clinical trials in acute infectious diarrhoea in adults have been published since those produced by the Food and Drug Administration (FDA), which date from 1977 [12]. Since acute diarrhoea in adults is generally self-limiting and rarely life-threatening or associated with critical dehydration, rapid resolution of the diarrhoeal episode is the treatment goal. For this reason, duration of the diarrhoeal episode rather than stool output is the standard outcome variable for studies in adults. Since the risk of dehydration is low, ORS are not normally necessary, and experimental medications can be evaluated as the primary treatment against placebo.

Diosmectite has been demonstrated to have several pharmacological properties which act clearly in the field of acute watery diarrhoea pathophysiology. A total of 6 randomised comparative studies have evaluated the efficacy of diosmectite in the treatment of acute diarrhoea in adults.

One pivotal study initiated by Ipsen [7], was conducted for the assessment of anti-diarrhoeal agents and conformed to a rigorous randomised, placebo-controlled, blinded design. This study showed a significant benefit of diosmectite versus placebo, which was of clinical relevance.

CCI [redacted]

There is no international consensus for the treatment by an antidiarrheal agent, in adult suffering from mild to moderate acute diarrhoea in adults. In addition placebo-treated subjects are not at risk in the study, owing to the fact that the disease is self-limiting and because patients with alarm symptoms will be excluded from the study. In the absence of alarm symptoms, there is no need for an antimicrobial agent (antibiotic).

CCI [redacted].

## 2.2 Study Objectives

The primary objective of the study is to demonstrate that diosmectite efficacy is superior to placebo regarding the time to recovery of an acute diarrhoea episode presumed of infectious origin in adult subjects.

The secondary objectives of the study are as follows:

- To demonstrate that diosmectite efficacy is superior to placebo regarding other efficacy criteria.
- To assess the clinical tolerance of diosmectite versus placebo

# 3 STUDY DESIGN

## 3.1 General Design and Study Schema

The study is a multicentre, prospective, double blind, placebo-controlled randomised comparative study. Efficacy and safety of diosmectite (administered at a dose and treatment regimen in line with diosmectite Summary of Product Characteristics (SmPC) for France (the daily dosage can be doubled at the beginning of treatment for acute episode), i.e. 2 sachets TID with a minimum of 24 sachets to be taken in 4 or 5 days and with a maximum of 48 sachets to be taken in 8 or 9 days) will be evaluated in adult subjects with a recent episode of acute diarrhoea presumed of infectious origin.

CCI [redacted]

In the previous phase IV study, the calculation of the number of subjects was based on a delta hours of 24 hours (difference of median time to recovery between the active group and the placebo group), while the delta actually found was 15 hours which was considered as clinically relevant.

The duration of the study treatment in this current study for each subject will be from 4 to 9 days.

At Visit 1, subjects will be randomised to 1 of the 2 treatment groups. Physical examination will be performed and a stool sample will be collected for microbiological examination. The treatment schema will consist of 2 sachets TID a day (i.e. in the morning, mid-day, and in the evening) with a minimum of 24 sachets taken within 4 or 5 days. The treatment will start at the investigator's office.

Subjects will receive a paper diary (diary evaluation booklet (DEB)) to be completed to record each stool and its consistency on a daily basis from inclusion until the end of the study. Symptoms such as nausea, vomiting, abdominal pain and anal irritation and study treatment intake will also be recorded. The patient will be contacted by the investigator or by a dedicated person of the investigator team on a daily basis to verify that the DEB is completed by the patient.

The treatment can be stopped in case of recovery according to the protocol definition after intake of 24 sachets within 4 or 5 days. At Visit 2 (Day 5 or Day 6), a physical examination will be performed and safety will be assessed.

In case the subject has not recovered from diarrhoea at Visit 2, he/she will prolong the treatment with a maximum of 48 sachets taken up to Day 8 or Day 9 at the latest. For these subjects only, a third visit (Visit 3; Day 9 or Day 10) is planned to perform a physical examination and assess safety.

## 3.2 Primary and Secondary Endpoints and Evaluations

### *3.2.1 Primary Efficacy Endpoint and Evaluation*

The primary efficacy endpoint is the time to recovery, defined as time from the 1st study treatment intake recorded in the electronic case report form (eCRF) to the first formed stool followed by a nonwatery stool, recorded in the DEB.

Consistency will be rated according to the Bristol scale [13].

### *3.2.2 Secondary Efficacy Endpoints and Evaluations*

The secondary endpoints are the following:

(a) abdominal pain intensity (rated with a 5-point ordinal scale: 0 = absent, 1= mild, 2 =moderate, 3 = severe, 4= very severe) per 12-hour period, recorded in the DEB

(b) time (hours, minutes) from diarrhoea onset to recovery defined as first formed stool followed by a nonwatery stool, recorded in the DEB

(c) time (hours, minutes) from first watery stool to the first formed stool, recorded in the DEB

(d) time (hours, minutes) from the 1st study treatment intake recorded in the eCRF to the last watery stool recorded in the DEB,

(e) number of stools, per 12-hour period, recorded in the DEB

(f) number of watery stools, per 12-hour period, recorded in the DEB

(g) percentage of subjects with associated symptoms such as nausea, vomiting, abdominal pain and anal irritation, per 12-hour period, recorded in the DEB*.

*Nausea, vomiting, abdominal pain and anal irritation, per 12-hour period will be recorded in the DEB. The percentage of subjects will not be recorded in the DEB.

### *3.2.3 Safety Endpoints and Evaluations*

The safety and tolerability of diosmectite will be assessed throughout the study by evaluating adverse events (AEs) recorded from subject from the time that the subject gives informed consent until 7 days after the end of the study treatment, vital signs measurements, and physical examination results, and concomitant medication usage.

## 3.3 Randomisation and Blinding

The secondary packaging is similar allowing the blinded conditions of the study to be maintained. Subjects and investigators will remain blinded to treatment assignment during the study.

The sponsor’s randomisation manager who is a statistician independent from the study will prepare the master list of randomisation numbers for this study. It will be produced in blocks, in a balanced 1:1 ratio. After eligibility is confirmed, at Visit 1 (Day 1), subjects will be assigned a randomisation number and to the associated treatment arm, in sequential order within each centre.

Each subject will be treated with the treatment pack allocated to this randomisation number.
The investigator will under no circumstances change the randomisation number and the treatment arm allocated to the subject.
Recruitment will stop once 854 subjects have been randomised. Randomised subjects who terminate their study participation for any reason before starting the treatment will retain their randomisation number (the randomisation number will not be reused). The next subject is given the next randomisation number.
Randomised subjects who leave the study early will not be replaced.

The sponsor's randomisation manager will keep the master list. A copy of this list will be confidentially supplied to the Unit in charge of drug packaging. The master list and the copy supplied to the Unit in charge of drug packaging will be kept confidential in a secure location. Access to the randomisation list must be restricted until authorisation is given to release it for final analysis.

## 3.4 Study Treatments and Dosage

IMP (active and placebo sachets) is not to be taken at the same time as other authorised drugs. A 2-hour period is recommended before or after diosmectite intake to avoid any potential interaction (adsorption) issue with other medication.

The test product, IMP, consists of a powder for suspension for oral use. The subject will take 2 sachets TID (in the morning, at mid-day, and in the evening). The first intake of IMP will be during the first visit. If the first visit occurs in the afternoon, only 4 sachets will be taken at Day 1, if the first visit occurs in the evening, only 2 sachets will be taken at Day 1. The morning intake can be until 11am, the mid-day intake until 6pm, the evening intake after 6pm However, the patient will have to take at least 24 sachets before Visit 2 at Day 5 or Day 6.

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

The comparator will be a placebo, consisting of a powder for suspension for oral use similar to the investigational product without the active substance.

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

The IMP will be packaged and delivered to the investigational sites/central or interim storage. A sufficient quantity of IMP will be supplied as well as an acknowledgement of receipt form. Code break envelopes will also be supplied.

The sponsor's representative will receive a Certificate of Analysis for which batch of IMP has been used under their study, and the Certificate of Compliance which reflects the product release statement.

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

- name, address and telephone number of the sponsor, contract research organisation (CRO) or investigator (the main contact for information on the product, clinical study and emergency unblinding,
- study number,
- pharmaceutical dosage form,
- route of administration,
- quantity of dose units,
- batch number,
- randomisation number,
- "For clinical study use only",
- storage conditions,
- expiry date,
- patient Number (this information will be completed by the investigator).

The label content will be adjusted to the different regulatory requirement of each country of the study.

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

## 3.5 Study Duration

This study will consist of an inclusion visit, i.e. Visit 1 (the subject will be randomised and start treatment that day) and a 4- to 9- day dosing period. In this study, subjects are expected to take the study treatment with a minimum of 24 sachets to be taken in 4 days to 5 days and with a maximum of 48 sachets to be taken in 8 or 9 days. Visit 2 will be on Day 5 or Day 6 and Visit 3 will be on Day 9 or Day 10.

The subject's participation in the study will be considered to have ended when the subject will have recovered from diarrhoea, defined as one formed stool followed by a nonwatery stool and when the last follow-up visit is performed.

The study will be considered to have started when the first subject has been enrolled/ provided signed informed consent.

## 3.6 Stopping Rules and Discontinuation Criteria

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events (SAEs) will be reviewed (see Section 8.1.4) as they are reported from the study centre to identify safety concerns. The study may be terminated by the sponsor at any time.

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

## 3.7 Investigational Medicinal Product Preparation Storage and Accountability

### *3.7.1 Investigational Medicinal Product Storage and Security*

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

### *3.7.2 Investigational Medicinal Product Preparation*

The investigator, or an approved representative (for example, pharmacist), will ensure that all IMP is dispensed by qualified staff members.

### *3.7.3 Investigational Medicinal Product Accountability*

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

The destruction of used and unused IMP (active or placebo) should be carried out only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. The study treatment will be destroyed either at site or in the interim storage facility or in a dedicated company that has agreement

for the destruction of IMP. In case it is not possible to destroy the IMP in the country, the IMP will be sent back to the sponsor for destruction.

### 3.8 Maintenance of Randomisation and Blinding

Two sets of individual sealed code break envelopes will be prepared by the sponsor's randomisation manager to enable emergency code break procedures for individual subjects without compromising the blind of the study. One set will be provided to the investigational site and one set will be provided to the Central Department of Pharmacovigilance at the sponsor.

Code break envelopes will only be opened in cases of medical emergency when treatment is dependent on knowledge of the IMP received. In the event of an SAE or unexpected AE, which requires the identification of the study treatment group, the investigator should first contact the Pharmacovigilance Representative outlined in the protocol. The investigator should then review the case status and all pertinent information with the representative from the Central Department of Pharmacovigilance who will consult with the Therapeutic Area Drug Safety physician prior to any code break.

Once it has been determined that knowledge of the treatment code is necessary, the investigator will ascertain the subject's identification number and randomisation number, and then break the blind for the subject concerned. The investigator will then sign date and provide reason for the code break on the Emergency Code break form, and on the code break envelope. Moreover, the investigator is allowed to unblind the trial randomisation code in case of emergency endangering a subject without prior consultation with the sponsor.

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

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

### 3.9 Source Data Recorded on the Case Report Form

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

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

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

Definition for source data and source documents are given below:

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

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

# 4 SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1 Inclusion Criteria

All subjects must fulfil all of following criteria to be included in the study:

(1) Provision of written informed consent prior to any study related procedures,

(2) male or female subject (outpatient) legally considered as an adult (age of majority). In Czech Republic the upper limit of age will be 70 years inclusive.

(3) subject has a diagnosis of acute diarrhoea presumed of infectious origin, defined as:

- the passage of 3 or more unformed loose or watery stools (rated according to the Bristol scale) per day without associated alarm symptoms*
- having started within 48 hours before Visit 1 (first study drug intake time).

(4) subject has, usually, normal bowel habits, (Rome III criteria) ** , i.e. at least 3 stools per week and no more than 3 stools per day,

(5) subject must be willing and able to comply with study restrictions and willing to return to the clinic for the follow up evaluation(s) as specified in the protocol.

*Symptoms considered as alarm symptoms are identified in the exclusion criteria (1)

**Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional Bowel Disorders. Gastroenterology 2006; 131:1480–91.

## 4.2 Exclusion Criteria

Subjects will not be included in the study if they meet:

- **Exclusion criteria related to the acute diarrhoea episode:**

(1) At least one of the following alarm symptoms*

- bloody diarrhoea*,
- pus in the stools*,
- fever ≥38.0°C*,
- moderate or severe dehydration according to World Health Organisation (WHO) definition, requiring intravenous (IV) rehydration*,
- repeated vomiting*
- persistent abdominal pain*

*These symptoms are considered as alarm symptoms

(2) other episode of acute watery diarrhoea within the previous 30 days,

(3) persistent diarrhoea, defined as acutely starting episode of diarrhoea lasting more than 14 days,

(4) history of chronic diarrhoea (Rome III criteria); i.e. 3 or more loose or watery stools per day for at least 12 weeks, consecutive or not, in the preceding 12 months,

(5) traveller's diarrhoea defined as a diarrhoeal episode due to contamination experienced by subjects having travelled in at risk countries, or coming from abroad and experiencing locally an acute diarrhoea episode, occurring usually within the first 2 weeks of the stay in a foreign environment.

- **Exclusion criteria related to drugs:**

(6) Diarrhoea suspected to be induced by drug for example:
  - antibiotic therapy, including Clostridium difficile-induced diarrhoea, within 1 week before entry in the study,
  - laxative agent
  - thyroid hormone (at a nonstabilised dosing),
  - colchicine intake, etc… (See Appendix 1)

(7) anti-diarrhoeal agent intake during the last month,
(8) any subject requiring repeated intake of a drug with a narrow therapeutic margin (for example, digoxin, theophylline, etc…) (See Appendix 2),
(9) history of hypersensitivity to diosmectite or its excipients or placebo components,
(10) subject likely to require treatment during the study with drugs that are not permitted by the study protocol (for example, antibiotic agent, anti-diarrhoeal agent, antiemetic drug, antispasmodic drug),
(11) use of any investigational medication within the last 30 days before entering this study,
(12) subject who previously entered in a clinical study within the past 30 days.

- **Other digestive exclusion criteria:**

(13) History of gastric or intestinal resection, vagotomy,
(14) known digestive malabsorption disease, including coeliac disease
(15) known lactose intolerance,
(16) any suspicion of abdominal surgery need,
(17) known inflammatory bowel disease.

- **Other exclusion criteria:**

(18) Known Human immunodeficiency virus (HIV) positive status,
(19) known or suspected immunosuppression,
(20) known severe renal or hepatic insufficiency,
(21) Uncontrolled diabetes of all types and non insulin dependant diabetes during first 6 months of medical treatment and other known endocrine disease,
(22) history of, or known current, problems with alcohol abuse and/or known drug addiction (cocaine, heroin, hashish…),
(23) previous enrolment in this study,
(24) any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude,
(25) Pregnant or lactating women.

## 4.3 Subject Withdrawal Criteria and Procedures

In accordance with the Declaration of Helsinki (in accordance with the applicable country's acceptance), each subject is free to withdraw from the study at any time and for any reason. The investigator and/or subject will be asked to perform/attend a final visit at any time in case of withdrawal, whatever the reason. The investigator also has the right to withdraw a subject from the study in the event of concurrent illness, AEs, or other reasons concerning the health or well-being of the subject, or in the case of lack of cooperation. In addition, a subject may be withdrawn from the

study as described in Section 3.6. Should a subject decide to withdraw from the study after administration of IMP, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (see Section 5.2.4) 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.

# 5 STUDY PROCEDURES

## 5.1 Study Schedule

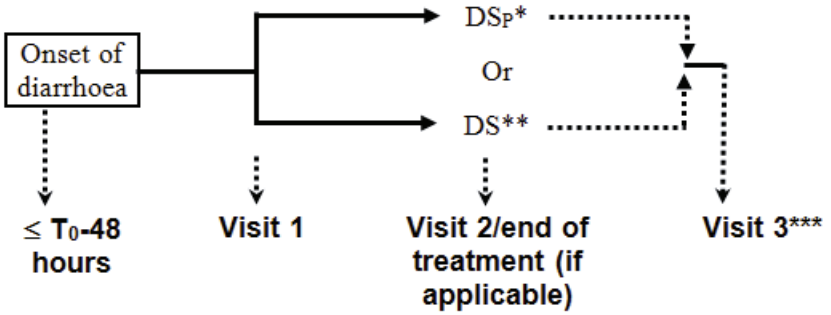
**Table 2 Study Schedule**

| Visit (Day) | Visit 1 | Visit 2 (Day 5 or 6) | Visit 3 (Day 9 or 10) | Early withdrawal |
|---|---|---|---|---|
| Informed Consent | X | | | |
| Demographic Data | X | | | |
| History of current acute diarrhoea episode | X | | | |
| Medical and surgical history | X | | | |
| Prior and concomitant medications for acute diarrhoea episode | X | X | X | X |
| Physical Examination | X | X | X | X |
| Vital Signs | X | X | X | X |
| Eligibility criteria | X | | | |
| Randomisation | X | | | |
| Study drug administration | X[a] | X[b] | X[c] | X |
| Patient diary (DEB) delivery/verification/collection | X | X | X | X |
| Visit status | X | X | X | X |
| Concomitant/surgical procedures | | X | X | X |
| Adverse events | X | X | X[d] | X |
| Prior and Concomitant Medications/ Non drug Therapies excluding those taken for acute diarrhoea episode | X[e] | X | X | X |
| Faecal sampling and results for microbiology analysis | X[f] | X[g] | | |
| Faecal virological results | | X | | |

a The first treatment must be taken during Visit 1. It will be taken in the morning, mid-day or in the evening depending on the time of Visit 1. The morning intake can be until 11am, the mid-day intake until 6pm, the evening intake can be after 6pm.
b a minimum of 24 sachets should be taken within 4 or 5 days
c a maximum of 48 sachets should be taken within 8 or 9 days
d reported by the subject until 7 days after the end of the study treatment
e taken within 30 days preceding Visit 1
f A fresh stool will be collected as soon as possible after inclusion
g faecal results will be recorded at Visit 2

A summary of the study design is presented in Figure 1.

**Figure 1 Study Design**




**D1**
- Physical Examination
- Inclusion /randomisation (= T0)
- Start of treatment
- Stool sample prescription for microbiological examination
- Start of subject's diary (DEB)

**D 5 or 6**
- Physical examination
- Safety
- End of treatment (if applicable)
- End of subject's diary (DEB) (if recovery)

**D 9 or 10**
- Physical examination
- Safety
- End of treatment (At $D_8$ or $D_9$ at the latest)
- End of subject's diary (DEB)***

* $DS_P$ = Placebo

** DS = Diosmectite

*** Only for subjects who did not recover by Visit 2

A summary of the chart for the Bristol scale is presented in Table 3.

**Table 3 Chart for Bristol scale**

| **Bristol Scale** | **Subject Inclusion** | **Subject Recovery (first formed stool followed by a nonwatery stool)** | |
|---|---|---|---|
| Type | Diarrhoea (Loose or watery stool) | First formed stool | Nonwatery stool |
| 1 | | X | X |
| 2 | | X | X |
| 3 | | X | X |
| 4 | | X | X |
| 5 | | | X |
| 6 | X | | |
| 7 | X | | |

## 5.2 Study Visits

### *5.2.1 Visit 1 (Procedures for Enrolment, Day 1)*

A signed and dated informed consent form will be obtained before screening procedures. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Subjects will acknowledge and agree to the possible use of this information for the study by giving informed consent.
After informed consent is obtained, at enrolment, subjects will be allocated a subject number. All enrolled subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required.

Enrolment (Visit 1) will take place within 48 hours after onset of diarrhoea. The following assessments will be performed:

- eligibility check (inclusion/exclusion criteria),
- demographic data (date of birth/age and sex will be collected according to individual country requirements),
- medical and surgical history, including ongoing medical conditions
- history of the current acute diarrhoea episode including:
  - date and time (hours, minutes) of first watery stool,
  - number of stools including number of watery stools and for each 12h period during the last 24 hours,
  - presence of other associated symptoms for the last 24 hours: nausea, vomiting, abdominal pain, anal irritation.
- physical examination,
- vital signs (blood pressure and heart rate in sitting position, respiratory rate, body temperature, body height and weight),
- one faecal sampling for microbiological examination to be collected as soon as possible after inclusion,
- prior and concomitant medications/non-drug therapies (excluding those taken for acute diarrhoea episode) taken within 30 days preceding the enrolment/inclusion visit,
- prior and concomitant medications for acute diarrhoea episode

Following confirmation of eligibility for the study, subjects will be given a randomisation/treatment allocation number and allocated to receive either diosmectite or placebo as specified in Section 6.1.

- collection of AEs,
- study treatment unit will be delivered to the subject according to the randomisation procedure,
- visit Status will be recorded
- start of treatment at the centre: time of first intake of study treatment (data to be recorded in the eCRF).
- the DEB and information for use will be delivered to the subject. Refer to Section 5.2.5 for details to be recorded in DEB

Next visit will be performed after at least 24 sachets have been taken (i.e. 4 or 5 days after the first visit (i.e. Day 5 or Day 6)).

Under no circumstances will subjects be enrolled more than once.
Each investigator will also maintain a record of all subjects enrolled into the study (i.e. who signed the informed consent form). Records up to the time of premature termination should be completed. In the event that the subject was not receiving IMP, the primary reason will be recorded.

### *5.2.2 Visit 2 (follow-up or End of study, Day 5 or Day 6)*

The following procedures will be performed:

- Adverse events will be reported by subject since the last visit and will be collected.
- The Investigator will check in the DEB if clinical data were appropriately recorded and if the study drug was appropriately used.
- Any change in the concomitant medication and/or surgical procedures since Visit 1 will be checked and recorded in the eCRF.
- A physical examination and body weight measurement will be performed.
- Vital signs (blood pressure, heart rate in sitting position, respiratory rate, body temperature and body weight) will be checked.
- Faecal microbiological results will be recorded
- Visit Status will be recorded

In case of recovery, the study treatment will be stopped. A last visit (Visit 3) will be planned at Day 9 or 10 for subjects who did not recover by Visit 2

### *5.2.3 Visit 3 (End of study if patient is not recovered at Visit 2, Day 9 or Day 10)*

- Adverse events will be reported by subjects since the last visit and will be collected until 7 days after the last treatment intake.
- Any change in the concomitant medication and/or surgical procedures since Visit 2 will be checked and recorded in the DEB.
- A physical examination and body weight measurement will be performed.
- Vital signs (blood pressure, heart rate in sitting position, respiratory rate body temperature and body weight) will be checked.
- The Investigator will check in the DEB if clinical data were appropriately recorded and if the study drug was appropriately used. A copy of the DEB will be kept in the subject's file and the original will be sent to the Sponsor (Data Management).
- Visit Status will be recorded

Treatments units with used and unused sachets will be kept by the investigator.

### *5.2.4 Early Withdrawal Visit*

- Adverse events will be reported by subjects since the last visit and will be collected until 7 days after the last treatment intake.
- Any change in the concomitant medication and/or surgical procedures since the previous visit will be checked and recorded in the DEB.
- A physical examination and body weight measurement will be performed.
- Vital signs (blood pressure, heart rate in sitting position, respiratory rate, body temperature and body weight) will be checked.

- The Investigator will check in the DEB if clinical data were appropriately recorded and if the study drug was appropriately used. A copy of the DEB will be kept in the subject's file and the original will be sent to the Sponsor (Data Management).

In case of either:
- impaired general health condition
- and/or moderate or severe dehydration
- and/or fever above 38°C
- and/or pus or blood in the stool
- and /or positive microbiological finding for Entamoeba histolytica or Giardia/Lamblia or Shigella in stool, the subject will be withdrawn from the study and an effective rehydration therapy and/or an anti-parasitic or antibiotic treatment will be immediately given accordingly.

If the subject is discontinued from the study (i.e., ceases participation in the study prior to completion of the protocol), the reason will be recorded in the eCRF. Withdrawal due to AEs (see Section 8.1.2) should be distinguished from other conditions for withdrawal. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow up (if required) for such subjects, and document the course of the subject's condition.

In all cases, the investigator must ensure the subject receives appropriate medical treatment (i.e. need for IV rehydration, and/or antiparasitic, and/or antibiotic therapy) and follow up to determine the final outcome if the period of the trial is over.

### *5.2.5 Diary Evaluation Booklet (DEB)*

The primary endpoints will be recorded in the DEB. The subject will be asked to record in the DEB each day, including at Day 1, the following data until the next visit: date, time of onset and consistency of stools (according to the Bristol scale; see Appendix 3, presence of symptoms such as nausea, vomiting, abdominal pain, anal irritation, and study drug consumption (number of sachets taken each day). See also Section 7.4.

# 6 TREATMENT OF SUBJECTS

## 6.1 Study Drugs Administered

At enrolment, subjects will be allocated a subject number. Following confirmation of eligibility for the study, subjects will be allocated to either diosmectite or placebo.

The regimen below will be 2 sachets* TID:

- 2 sachets in the morning,
- 2 sachets at mid-day,
- 2 sachets in the evening.

*Each sachet to be taken in half a glass of water

Subjects will receive a box that contains 48 sachets of study medication.

A minimum of 24 sachets is to be taken within 4 or 5 days and then until recovery (with a maximum of 48 sachets taken within 8 or 9 days). The acute diarrhoea episode will be considered to have resolved after the subject has passed one formed stool followed by a nonwatery stool.

- **From Day 1 to Day 4 or Day 5**:
  - mandatory treatment period = 24 sachets
- **From Day 5 to Day 8 or Day 9:**
  - if one formed stool is followed by a nonwatery stool, i.e. recovery, the treatment is stopped,
  - in any case, treatment stops after a maximum of 48 sachets have been taken

Each randomised subject will receive a numbered box. The box labels will comprise a detachable part on which the box number and protocol number will be written.

At Visit 1, when the study drug box is given to the subject, the investigator will stick the detachable part of the label on a study treatment log.

### *6.1.1 Diosmectite*

Diosmectite consists of sachet of powder for suspension for oral use.

**Diosmectite** will be presented in sachets according to the following composition:

- active substance:
  - diosmectite: 3 g
- other components:
  - vanillin, saccharin sodium and glucose monohydrate

Each sachet will be mixed with water prior to administration

### *6.1.2 Placebo*

**Placebo** will be presented in sachets according to the following composition:

- titan dioxide, spray dried liquid glucose, vanillin, saccharin sodium, glucose monohydrate,
- caramel colouring E 150 B.

## 6.2 Concomitant Medication/Therapy

Any prior or concomitant therapy or medication given to a subject within 30 days before IMP administration or during IMP administration will be indicated on the eCRF. Dose and generic name or tradename will be indicated.

The following concomitant medications are not permitted during this study:

- Antibiotics

- Anti-diarrheal agents
- Antiemetic drugs
- Antispasmodic drugs

All forbidden concomitant medication are listed in Appendix 1 and Appendix 2.

The following hydration and dietary advices will be provided if the subject does not have signs of dehydration:
• have frequent water intake and small meals, throughout the day:
- intake mixed low fiber foods such as eggs (white mainly), white meats, beef, fish, cheese, white rice, potatoes, white bread, pasta, semolina, tapioca, cassava,...
• avoid canned fruit juices, beverages with sorbitol, alcohol, coffee, tea, or other caffeinated beverages, fatty foods, fried meats or fish, high fibre-rich foods such as oily seeds (e.g. almonds, peanuts, etc.), fruits, beans, lentils, chickpeas, raw vegetables.

In case of mild dehydration, food intake could be started after correction of dehydration, using Oral Rehydration Salts (ORS) therapy according to World Health Organisation (WHO)/United Nations Children's Fund (UNICEF) recommendation (Clinical management of acute diarrhoea WHO/UNICEF joint statement 2004).

## 6.3 Procedures for Monitoring Subject Compliance

The investigator will be responsible for monitoring subject compliance. The subject can be withdrawn from the study at any time if the investigator or the sponsor determines that he/she is not in compliance with the study protocol.
Details of compliance, deviations from the scheduled amount of IMP intake regarded as major protocol violations will be detailed in the statistical analysis plan (SAP).
Where a subject is consistently noncompliant with IMP intake they should be discontinued from IMP/withdrawn from the study. Please refer to Section 4.3 for the criteria for discontinuing the subject from IMP.

# 7 ASSESSMENT OF EFFICACY

For the treatment schedule in this study, refer to the schedule in Table 2. For characteristics of subject recovery, refer to Table 3.

## 7.1 Primary Efficacy Endpoint and Evaluation

The primary endpoint will be the time to recovery (hours) defined as the time (hours, minutes) from the 1st study treatment intake recorded in the eCRF to the first formed stool recorded in the DEB (this formed stool must have been followed by a nonwatery stool). Consistency will be rated according to the Bristol scale [13]. See Appendix 3 for the Bristol scale.

## 7.2 Secondary Efficacy Endpoints and Evaluations

The secondary endpoints are:

- abdominal pain intensity (rated with a 5-point ordinal scale: 0 = absent, 1= mild, 2 =moderate, 3 = severe, 4= very severe) per 12-hour period,
- time (hours, minutes) from diarrhoea onset to recovery defined as 1st formed stool followed by a nonwatery stool,
- time (hours, minutes) from first watery stool to the first formed stool,
- time (hours, minutes) from the 1st study treatment intake to the last watery stool,
- number of stools, per 12-hour period,
- number of watery stools, per 12-hour period,
- percentage of subjects with associated symptoms such as nausea, vomiting, abdominal pain, and anal irritation, per 12-hour period.

## 7.3 Microbiological Tests

A fresh stool will be collected as soon as possible after inclusion for microbiological laboratory testing (for virology, bacteriology and parasitology testing) in order to determine the microbiological status of this acute diarrhoea episode , i.e. the absence/presence of the following faecal pathogens:

<u>Virology testing</u>

- rotavirus,
- adenovirus,
- norovirus,

<u>Bacteriology and parasitology testing</u>

- enteropathogenic and Enterotoxigenic Escherichia Coli (E. coli),
- staphylococcus aureus,
- shigella,
- salmonella,
- campylobacter,
- yersinia enterocolitica,
- amoeibiasis (entamoeba histolytica),
- giardia / lamblia.

Details of the methodology and technical specifications will be provided in the laboratory manual located in the Investigator Site File and in the TMF.

Laboratory test results provided by the lab will be recorded in the laboratory results section of the eCRF by the investigator at Visit 2.

## 7.4 Methods and Timing of Assessing, Recording, and Analysing Efficacy Data

The subject will be asked to complete, each day from Day 1 (day of Visit 1) to the end of the treatment visit (Visit 2 (Day 5 or Day 6) or Visit 3(Day 8 or Day 9)), the DEB with the following information:

- Stools:
  - date and time to onset,
  - consistency rated as either watery, loose, formed or hard (according to the Bristol scale; see Appendix 3),
- Presence or not of an episode for each 12-hour period:
  - nausea,
  - vomiting,
  - abdominal pain
  - anal irritation.
- abdominal pain intensity (rated with a 5-point ordinal scale: 0 = absent, 1= mild, 2 =moderate, 3 = severe, 4= very severe)
- Study drug consumption (number of sachets per day)

Methods for assessing efficacy data are described above in Section 7.1 and Section 7.2. Timing of efficacy assessments are discussed in Section 5. Procedures for recording efficacy data are discussed in Section 14.1, and methods of analysis are discussed in Section 10.4.5.

# 8 ASSESSMENT OF SAFETY

## 8.1 Adverse Events

Adverse events will be monitored from the time that the subject gives informed consent and throughout the study until 7 days after the end of study treatment (see Section 3.5 for a definition of the study duration) and will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 8.1.2.

### *8.1.1 Definition of an Adverse Event*

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

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

Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the baseline diarrhoea.

These signs and symptoms should only be reported as AEs/SAEs (depending on the investigator's judgement) if they are:

- Judged by the investigator to be unusually severe or accelerated diarrhoea, or

- If the investigator considers the deterioration of diarrhoea signs and symptoms to be caused directly by the IMP.

If there is any uncertainty about an AE being due solely to the diarrhoea under study, it should be reported as an AE/SAE as appropriate.

### *8.1.2 Categorisation of Adverse Events*

*8.1.2.1 Intensity Classification*

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

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

*8.1.2.2 Causality Classification*

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

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

*8.1.2.3 Assessment of Expectedness*

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

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

*8.1.2.4 Laboratory Test Abnormalities*

Not applicable.

*8.1.2.5 Abnormal Physical Examination Findings*

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

*8.1.2.6 Other Investigation Abnormal Findings*

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

### *8.1.3 Recording and Follow up of Adverse Events*

At each visit, the subject should be asked a nonleading question such as: "How have you felt since starting after the last assessment?"

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to IMP, will be recorded on the AE page(s) of the CRF/eCRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the study, or exacerbation's of pre-existing illnesses should be recorded.

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

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

### *8.1.4 Reporting of Serious Adverse Events*

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

A SAE is any AE that:

(1) Results in death.

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

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

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

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

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

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

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

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

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

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

- Study number
- Centre number
- Subject number
- AE
- Investigator's name and contact details

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

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

### *8.1.5 Pregnancy*

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

Information regarding pregnancies must be collected on the adverse event page of the eCRF and reported to the sponsor as an SAE. The sponsor will request further

information from the investigator as to the course and outcome of the pregnancy using the Standard Pregnancy Outcome Report Form.

#### *8.1.6 Deaths*

All AEs resulting in death either during the study period or within 7 days after the last dose of IMP, must be reported as an SAE within 24 hours of the investigator's knowledge of the event.
The convention for recording death is as follows:

- adverse event term: lead cause of death,
- outcome: fatal.

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

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

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the IMP (see Section 4.3).
If the IMP is discontinued due to a SAE, it must be reported immediately to the sponsor's designated representative (see Section 8.1.4).
In all cases, the investigator must ensure the subject receives appropriate medical follow up (see Section 8.1.3).

#### *8.1.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators*

The sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the study to the CA, IECs and other investigators concerned by the IMP. Reporting will be done in accordance with the applicable regulatory requirements.

### 8.2 Physical Examination

Physical examinations, including body weight, will be conducted at Baseline (Visit 1), at Visit 2 and at Visit 3 if applicable. Body height will be measured at Baseline.
Any clinically significant physical examination findings (abnormalities) observed during the study will be reported as AEs. Any physical examination findings (abnormalities) persisting at the end of the study will be followed by the investigator until resolution or until reaching a clinically stable endpoint.

### 8.3 Vital Signs

Blood pressure and heart rate will be assessed with an automated device so that measurements are independent of the observer. Blood pressure and heart rate will be recorded after five minutes rest in sitting position. Absolute values and change from Baseline will be analysed.
Respiratory rate, body temperature, body height (only at visit 1) and body weight will be recorded.

# 9 ASSESSMENTS OF PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics is not applicable to this study and pharmacodynamics is not assessed in this study.

# 10 STATISTICS

## 10.1 Analyses Populations

The following population will be used during statistical analyses:

a) **Intent to treat (ITT) population**: all randomised subjects analysed according to the arm to which they were randomised.
b) **Safety population**: all randomised subjects with at least one dose of study medication analysed according to the actual treatment received
c) **Modified Intent to treat (mITT) population**: all randomised subjects who received at least one dose of study medication and have at least one efficacy assessment for the primary endpoint*. Subjects will be analysed according to the arm to which they were randomised.
d) **Per protocol (PP) population**: all subjects in the mITT population for whom no major protocol violations/deviations occurred.

*The efficacy assessment will be based on the DEB; therefore subjects who have not filled in the DEB will be excluded from the efficacy analysis

### *10.1.1 Populations Analysed*

The primary analysis based on the primary efficacy endpoints will be evaluated based on the ITT population. In addition, analysis will be performed on mITT and PP population as secondary.
Secondary efficacy endpoints as well as demographics characteristics will be performed on the ITT population. In addition, analysis will be performed on the PP population as secondary.
The analyses of safety data will be performed on the Safety population.

### *10.1.2 Subject Allocation and Reasons for Exclusion from the Analyses*

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

## 10.2 Sample Size Determination

Assuming a median time to recovery of 55 hours in the active group and 70 hours in the placebo group (corresponding to a difference of 15 hours as evidenced in the Khediri et al study [7], 363 evaluable subjects per treatment group (726 in total) will be required in order to detect such a difference using a two-sided Gehan- Wilcoxon test at a significance level of 5% and a power of 80%.
It is assumed a maximum of 5% subjects prematurely withdrawn without recovery and a maximum of 10% nonevaluable subjects (because of poor/incomplete diary (DEB) completion).
Accordingly, 854 subjects (427 per treatment group) have to be randomized in order to achieve an 80% power

## 10.3 Significance Testing and Estimations

All statistical tests will be performed two-sided with a type I error rate set at (5%).
For any efficacy endpoints, the 95% confidence interval (CI) of the difference between treatment groups will be calculated when appropriate.

## 10.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external CRO, managed by the sponsor's Biometry Department.
A SAP describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document.
The SAP will detail the rules and conventions used to compute the derived analysis variables and to handle missing data
Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version 9.2 or higher).
Descriptive statistics will be presented as follows:

- continuous variables: number of observations, number of missing values mean, standard deviation (SD), median, percentiles, minimum and maximum,
- dichotomous or categorical variables: frequency and percentage of each of the categories.

No adjustments for multiple testing are planned.
All study data will be at least presented in listings.

### *10.4.1 Demographic and Other Baseline Characteristics*

In order to ensure balance of treatment groups, descriptive summary statistics (n, mean, SD, median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant disease (ongoing medical history, prior medications, baseline symptoms, presence/absence of faecal pathogens), season of randomisation (summer/winter season), etc…) will be presented by treatment group and overall for the ITT population.

### *10.4.2 Homogeneity of Treatment Groups*

Descriptive statistics for demographic and other baseline characteristics will be tabulated for each treatment groups, 95% CIs may be calculated for baseline characteristics.

### *10.4.3 Subject Disposition and Withdrawals*

The numbers and percentages of subjects enrolled and included in populations will be tabulated by country. The reasons for subject exclusions from each of the populations will also be tabulated. In addition, the numbers of subjects who were randomised, discontinued and completed will be tabulated by treatment group. Primary reasons for discontinuation of study treatment will be tabulated.

### *10.4.4 Pharmacokinetic Data*

No pharmacokinetic data analysis will be performed.

### *10.4.5 Efficacy Evaluation*

The primary analysis of efficacy data will be performed on the ITT population. Additionally, for the main efficacy variable, a supportive analysis using mITT and PP populations will be carried out.

The primary endpoint (time from the first study treatment intake ($T_0$)) to recovery defined as 1st formed stool followed by a nonwatery stool (in hours), will be analysed using a time to event methodology.
Time to event data will be analysed by using survival methods. The results will be presented both in summary tables and graphically in Kaplan-Meier plots and the estimated medians and quartiles will be provided.
The comparison between the 2 groups of treatment will be performed using Gehan-Wilcoxon test. Subject prematurely withdrawn or ending the study without recovery will be censored (not responder).
Sensitivity analyses will be conducted to further explore the primary efficacy endpoint adjusting by country.
A cox model [14] will be used to assess the impact of other factors like season of randomisation, absence/presence of faecal pathogens on the treatment effect.

The analysis regarding secondary efficacy endpoints will be performed on the ITT population; supportive analysis using PP population will be carried out.
The secondary efficacy variables are:

a) Abdominal pain intensity per 12-hour period.
b) Time (hours, minutes) from diarrhoea onset to recovery defined as 1st formed stool followed by a nonwatery stool.
c) Time (hours) from first watery stool to the first formed stool.
d) Time (hours) from the 1st study treatment intake to the last watery stool.
e) Number of stools, per 12-hour period.
f) Number of watery stools, per 12-hour period.
g) Percentage of subjects with associated symptoms such as nausea, vomiting, abdominal pain and anal irritation, per 12-hour period.

Missing data of secondary efficacy variables will not be replaced.
The secondary endpoints related to time to event (efficacy variables b, c and d) will be analysed using the same methodology as for the primary efficacy endpoint.
Regarding the secondary endpoints based on number of stools per 12-hour period, a repeated measurement model of number of stools during the post baseline period will be fitted using the analysis of covariance (ANCOVA) method if data warrant. The model will include as fixed effects number of stools 24 hours before randomisation (baseline), treatment, time point (12-hour period) and the treatment by time point interaction effect. The residual variance-covariance pattern will be fitted using an unstructured matrix. In addition a cumulative number of stools per 12-hour period will be presented graphically.
The same analysis will be performed for number of watery stools. The model will include, as fixed effects, number of watery stools 24 hours before randomisation, treatment, time point (12-hour interval) and the treatment by time point interaction effect.
Regarding the efficacy endpoints related to binary data, a general linear mixed model will be fitted if data warrant in order to evaluate the treatment effect at each 12-hour period, according to the same methodology as described above.
In addition point estimate will be tabulated by treatment group and overall with their corresponding two-sided 95% CIs and when appropriate in terms of mean, SD, median and interquartile as well as the range.
More details will be given in the SAP.

### *10.4.6 Adjustment for Country/Centre Effect*

Adjustment for country effect will be planned for the analysis of primary efficacy by using country as covariates in the cox model.

### *10.4.7 Safety Evaluation*

Safety evaluation will be performed in the Safety population.
All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the Safety population.
AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA; current version at time of database lock) and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by subject, system organ class and preferred term.
Incidence of all reported AEs/treatment emergent AEs (TEAEs) and SAEs will be tabulated by treatment group and overall. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of study medication.
A TEAE is defined as any AE that occurs during the active phase of the study if:

- it was not present prior to receiving the first dose of IMP, or
- it was present prior to receiving the first dose of IMP but the intensity increased during the active phase of the study, or
- it was present prior to receiving the first dose of IMP, the intensity is the same but the drug relationship became related during the active phase of the study.

Treatment emergent AEs will be flagged (*) in the AEs listings.
Concomitant medication will be coded by using WHO Drug Dictionary and will be summarised by treatment group and overall with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.
Summary statistics (mean, median, SD and range as appropriate) by treatment group and overall will be presented for vital signs (blood pressure, heart rate in sitting position, respiratory rate, body weight at each assessment with change from Baseline.

## 10.5 Subgroup Analyses

Descriptive statistics for efficacy evaluation may be provided by country, season, absence/presence and type of faecal pathogens.
Descriptive statistics for safety evaluation will be provided within each category of the following variables:

- country,
- season,
- absence/presence and type of faecal pathogens.

Details of the above will be specified in the SAP.

## 10.6 Interim Analyses

No interim analysis will be performed.

# 11 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

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

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

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

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

## 12.1 Protocol Amendments and Protocol Deviations and Violations

### *12.1.1 Protocol Amendments*

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

### *12.1.2 Protocol Deviations, Violations, and Exceptions*

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

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

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

## 12.2 Information to Study Personnel

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

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

## 12.3 Study Monitoring

The investigator is responsible for the validity of all data collected at the site.
The sponsor is responsible for monitoring this data to verify that the rights and well-being of subjects are protected, that study data are accurate (complete and verifiable to source data) and that the study is conducted in compliance with the protocol, GCP and regulatory requirements.
Sponsor assigned monitors will conduct regular site visits. The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested. Adequate time and space for monitoring visits should be made available by the investigator.
The site must complete the eCRFs according to the sponsor monitoring manual, of the subject's visit and on an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The central study monitor at the sponsor will use functions of the Electronic Data Capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.
Whenever a subject name is revealed on a document required by the sponsor (for example, laboratory print outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

## 12.4 Audit and Inspection

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

## 12.5 Data Quality Assurance

Monitored eCRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.
Reasons should be given on the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the investigator by the monitor for clarification/correction. The investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

# 13 ETHICS

## 13.1 Compliance with Good Clinical Practice and Ethical Considerations

This study will be conducted in compliance with IECs/IRBs, informed consent regulations, the Declaration of Helsinki and ICH GCP Guidelines (Section 1.6).
In addition, this study will adhere to all local regulatory requirements.
Before initiating a study, the investigator/institution should have written and dated approval/favourable opinion from the IEC/IRB and local Regulatory Authority for the study protocol/amendment(s), written informed consent form, any consent form updates, subject emergency study contact cards, subject recruitment procedures (for example, advertisements), any written information to be provided to subjects and a statement from the IEC/IRB that they comply with GCP requirements. The IEC/IRB and local Regulatory Authority approval must identify the protocol version as well as the documents reviewed.
After IEC/IRB and local Regulatory Authority approval, changes will require a formal amendment. Once the study has started, amendments should be made only in exceptional circumstances. Changes that do not affect subject safety or data integrity are classified as administrative changes and generally do not require ethical approval. If ethically or substantially relevant aspects are concerned, the IEC/IRB and/or local Regulatory Authority must be informed accordingly and, if necessary, approval sought prior to implementation. Ethical approval on administrative changes will be obtained if required by local/site IEC/IRB.

## 13.2 Informed Consent

Prior to study entry, the investigator, or a person designated by the investigator, will explain the nature, purpose, benefits and risks of participation in the study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the IMP). Sufficient time will be allowed to discuss any questions raised by the subject.
The sponsor will provide a sample informed consent form. The final version controlled form must be agreed to by the sponsor and the IEC/IRB and must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the investigator. The investigator will supply subjects with a copy of their signed informed consent.
The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. In this instance approval should always be given by the IEC/IRB. It is the investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/well-being.
The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

### 13.3 Health Authorities and Independent Ethics Committees/Institutional Review Boards

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

### 13.4 Confidentiality Regarding Study Subjects

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

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

# 14 DATA HANDLING AND RECORD KEEPING

## 14.1 Data Recording of Study Data

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

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

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

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

## 14.2 Data Management

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

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

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

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

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

The coding of an AE, medical history and concomitant medication terms will be performed by a CRO, directed by the sponsor's Biometry Group, and reviewed and approved by the sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA.

### 14.3 Record Archiving and Retention

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

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

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

# 15 FINANCING AND INSURANCE

## 15.1 Contractual and Financial Details

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

Financial Disclosure Statements will need to be completed for each investigator according to the local transparency requirement and legal guidelines and, if applicable, to the new European Transparency Initiative led by the EFPIA.

## 15.2 Insurance, Indemnity and Compensation

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

# 16 REPORTING AND PUBLICATIONS OF RESULTS

## 16.1 Publication Policy

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

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

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

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

## 16.2 Clinical Study Report

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

# 17 REFERENCES

1. Garthwright W., Archer D., Kvenberg J. Estimates of incidence and cost of intestinal infectious diseases in the United States; Public Health Rep. 1988;103: 107-15.
2. Guerrant RL, Hugues JM, Lima NL, Crane J. Diarrhoea in developed and developing countries, magnitude, special settings and etiologies. Rev of Infect Dis 1990; 12 suppl I: s41-50.
3. Thielman NM, Guerrant RL Acute infectious Diarrhoea N Engl J Med. 2004;350: 38-47
4. Avenclano P, Matson D., Long J., et al Costs associated with office visits for diarrhoea in infants and toddllers. Pediatric. Infect. Dis. J. 1993; 12: 897-902.
5. Faure C. Role of Antidiarrhoeal Drugs as Adjunctive Therapies for Acute Diarrhoea in Children. Int J Pediat. 2013;2013:612403
6. Guarino A1, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr. 2014 Jul;59(1):132-52.
7. Khediri F, Mrad AI, Azzouz M, Doughi H, Najjar T, Mathiex-Fortunet H, Garnier P, Cortot A (2011). Efficacy of diosmectite (Smecta®) in the Treatment of Acute Watery Diarrhoea in Adults: A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study. Gastroenterol Res Pract;783:196
8. Grim RE: Applied clay mineralogy. Mc Graw Hill, London .1968;51-125
9. Allen A, Leonard A: Mucus structure. Gastroenterol Clin Biol. 1985; 9(12 Pt 2):9-12.
10. Elmore AR: Final report on the safety assessment of aluminum silicate, calcium silicate, magnesium aluminum silicate, magnesium silicate, magnesium trisilicate, sodium magnesium silicate, zirconium silicate, attapulgite, bentonite, Fuller's earth, hectorite, kaolin, lithium magnesium silicate, lithium magnesium sodium silicate, montmorillonite, pyrophyllite, and zeolite. Int J Toxicol. 2003; 22 Suppl 1:37-102.
11. World Health Organization (2005), The treatment of diarrhoea. A manual for physicians and other senior health workers. In:WHO, Geneva.
12. US Food and Drugs Administration (1977) Guidelines for the clinical evaluation of anti-diarrhoeal drugs. In:FDA, Rockville, USA.
13. Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32(9):920-4.
14. Cox DR. Regression models and life tables J Roy Statist Soc B. 1972;34:187-220

# LIST OF APPENDICES

# Appendix 1 List of drugs prohibited at the time of study entry and leading to exclusion

Main drugs known to induce diarrhoea within the first days following the first intake (non-exhaustive list):

- alpha-glucosidase inhibitors: eg Acarbose
- biguanides: eg Metformin
- biliary acids (cheno-deoxycholic acid)
- bisphophonates
- prostaglandins
- protease inhibitors (for HIV)
- selective serotonin uptake inhibitors
- thyroid hormones (at a non-stabilised dosing)
- auranofin (gold salts)
- bepridil
- calcitonin
- captopril
- colchicin
- diacerein
- didanosin
- digoxin
- leflunomid
- methyldopa
- olsalazin
- orlistat
- propranolol
- quinidin
- ticlopidine

Any antiemetic drugs:

- Dopamine antagonists:
  - domperidone (Motilium)
  - olanzapine (Zyprexa)
  - droperidol, haloperidol, chlorpromazine, prochlorperazine
  - alizapride
  - prochlorperazine
  - metoclopramide
- Antihistamines (H1 histamine receptor antagonists):
  - cyclizine
  - diphenhydramine
  - dimenhydrinate
  - doxylamine
  - meclizine
  - mirtazapine
  - promethazine
  - hydroxyzine
- 5-HT3 receptor antagonists

- NK1 receptor antagonist:
- cannabinoids

Any anti-diarrhoeal drugs:

- Any strains of probiotic drugs approved for acute diarrhoea therapeutic management
- Antisecretory drugs:
  - racecadotril
- Motility-modifying drugs:
  - Opiates:
    - loperamide
    - diphenoxylate
    - diphenoxylate with atropine
    - paregoric tincture of opium
    - codeine
- Antimicrobial agents
  - nifuroxazide type
  - rilbroquinol & tiliquinol
- Adsorbents
  - Any therapeutic clays:
    - smectite, diosmectite,
    - attapulgite
- Other mucosal protectants and adsorbents
  - kaolin-pectin formulations
  - methylenic Lactoproteins
  - gelatin tannate
  - activated charcoal
  - bismuth subsalicylate
  - others
- Any other anti-diarrhoeal agents

Any Antibiotic Agents:

- **penicillins** : penicillin G, penicillin-VK, methicillin, nafcillin, oxacillin, ampicillin, amoxicillin, amoxicillin + clavulanic acid
- **cephalosporins** : cephalothin, cefazolin, cephapririn, cephalexin, cefacor, cefotetan, ceftriaxone, cefpirome, cefepime
- **fluroquinolones** : ciprofloxacin, levofloxacin, norfloxacin, moxifloxacin
- **aminoglycosides** gentamicin, tobramycin, amikacin, kanamycin, neomycin,
- **macrolides**: erythromycin, azithromycin, clarithromycin, clindamycin, dirithromycin
- **carbapenems**: ertapenem, imienem, meropenem
- **monobactams:**: aztreonam
- **other**: vancomycin, rifampicine, doxycycline, linezolid, tetracycline, trimethoprim, sulfamethoxazole, co-trimoxazole, metronidazole, tinidazole.

Any antispasmodic drugs such as:

- Dicycloverine hydrochloride
- Papaverine chlorhydrate
- Pinaverium bromure
- Mebeverine chlorhydrate
- Phloroglucinol
- Trimebutine maleate
- Dihexyverine chlorhydrate
- Clidinium bromure
- Alverine citrate

# Appendix 2 Narrow Therapeutic Index (NTI) drugs

Listing and Definition of Narrow Therapeutic Index or Range (NTI) Drugs

**NOTE: This was a sample list of drugs published by the FDA in 1988. Refer to official definition or contact specific drug manufacturer for accurate determination if a drug has a narrow therapeutic index or range.**

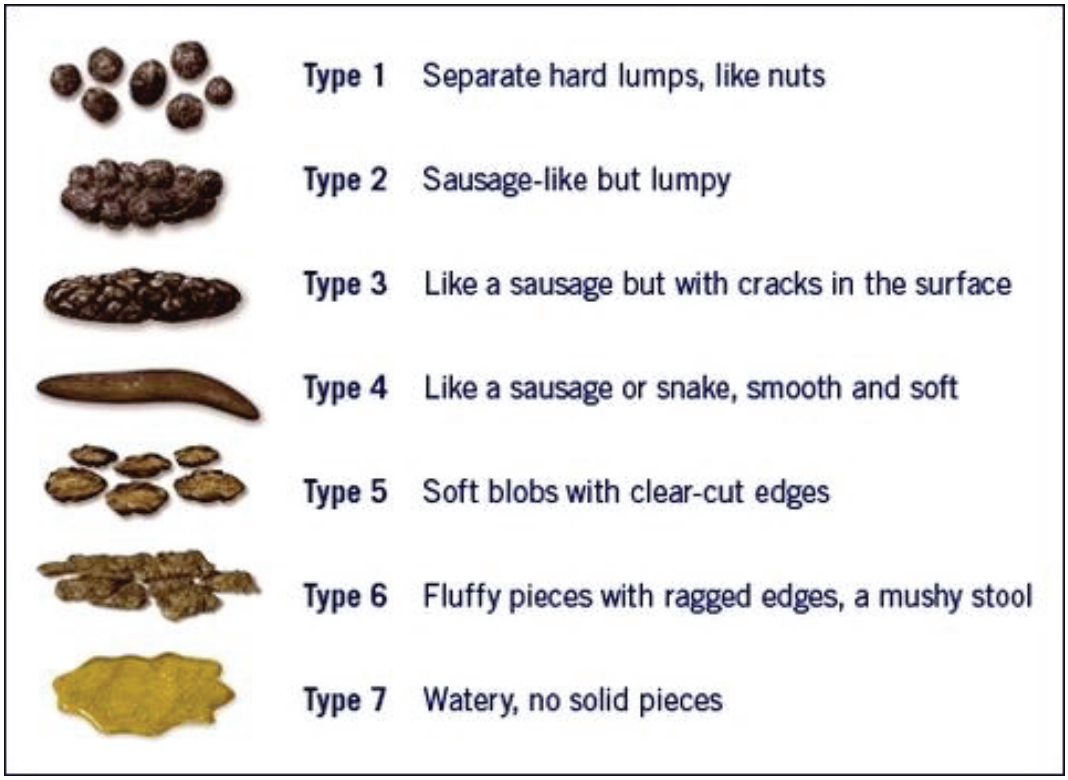
| | | | |
|---|---|---|---|
| Aminophylline | Carbamazepine | Clindamycin | Clonidine |
| Digoxin* | Disopyramide | Dyphylline | Guanethidine |
| Isoetharine mesylate | | Isoproterenol | Levoxyine* |
| Lithium Carbonate | | Metaporterenol | Minoxidil |
| Oxytriphylline | | Phenytoin | Prazosin |
| Primidone | | Procainamide | Quinidine gluconate |
| Theophylline | | Valproic Acid | |
| Valproate sodium syrup | | Warfarin sodium | |

*Also Pre 1938 Drug

**OFFICIAL DEFINITION**: Under Section 320.33(c) of Code of Federal Register 21, the US FDA defines a drug product as having a narrow therapeutic ratio as follows:

(a) there is less than a 2-fold difference in median lethal dose and median effective dose values, or
(b) there is less than 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and
(c) safe and effective use of the drug products require careful titration and Patient monitoring.

# Appendix 3 Bristol Stool Chart




- Types 1–2 indicate hard stool,
- Types 3 and 4 are the ideal stools (especially the latter), as they are easy to defecate while not containing any excess liquid,
- Types 5, 6 and 7 tend towards diarrhoea.

The subjects will be included if stool consistency is watery (Type 7) and/ or loose (Type 6) (See chart for Bristol scale below) (Acute diarrhoea episode is defined as the passage of 3 or more unformed (loose or watery) stools per day).

The subject will be considered to have recovered if the subject records a stool with a formed consistency corresponding to Type 1 to Type 4 (inclusive), followed by a nonwatery stool corresponding to Type 1 to 5 (inclusive) (See chart for Bristol scale below) (Time to recovery = Time (hours, minutes)) from the 1st study treatment intake to the first formed stool (this formed stool must have been followed by a nonwatery stool).

**Chart for Bristol scale**

| **Bristol Scale** | **Subject Inclusion** | **Subject Recovery (first formed stool followed by a nonwatery stool)** | |
|---|---|---|---|
| Type | Diarrhoea (Loose or watery stool) | First formed stool | Nonwatery stool |
| 1 | | X | X |
| 2 | | X | X |
| 3 | | X | X |
| 4 | | X | X |
| 5 | | | X |
| 6 | X | | |
| 7 | X | | |