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STATISTICAL AND ANALYSIS PLAN

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

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

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Clinical Statistics Manager or designee	PPD IPSEN Innovation 65, quai Georges Gorse 92 650 Boulogne Billancourt, FRANCE		
Clinical Study Co-ordinator	PPD IPSEN Innovation 65, quai Georges Gorse 92 650 Boulogne Billancourt, FRANCE		
Vice President Medical Development	PPD Ipsen Pharma SAS 65, quai Georges Gorse 92 650 Boulogne Billancourt, FRANCE		

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Study statistician	PPD BIOTRIAL Rue Jean-Louis Bertrand 35000 Rennes FRANCE		
Manager statistician	PPD BIOTRIAL Rue Jean-Louis Bertrand 35000 Rennes FRANCE		

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

History of Changes				
Old Version Number		Date Old Version	Date New Version	Reason for Change
Page	Section	Was	Is	

TABLE OF CONTENTS

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	Adverse Event
ANCOVA:	Analysis of Covariance
am	ante meridiem
ATC:	Anatomic Therapeutic Class
BMI	Body Mass Index
Bpm	Beats per minutes
CRF:	Case Report Form
CRO:	Contract Research Organisation
DEB	Diary Evaluation Booklet
e:	Electronic
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
ITT:	Intention-To-Treat
KM:	Kaplan-Meier
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	Modified Intention-to-Treat
PDD	Protocol Deviations Document
pm	Post meridiem
PP:	Per Protocol
PT:	Preferred Term
QC:	Quality Control
SAE:	Serious Adverse Event
SAP:	Statistical and Analysis Plan
SAS®:	Statistical Analysis System®
SEM:	Standard Error of the Mean
SmPC	Summary of Product Characteristics
SOC:	System Organ Class

SOP:	Standard Operating Procedure
TEAE:	Treatment Emergent Adverse Event
TID	Three times a day
WHO-DD:	World Health Organization – Drug dictionary

1 INFORMATION TAKEN FROM THE PROTOCOL

1.1 Study objectives

1.1.1 Primary objective

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.

1.1.2 Secondary objectives

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

1.2 Study design

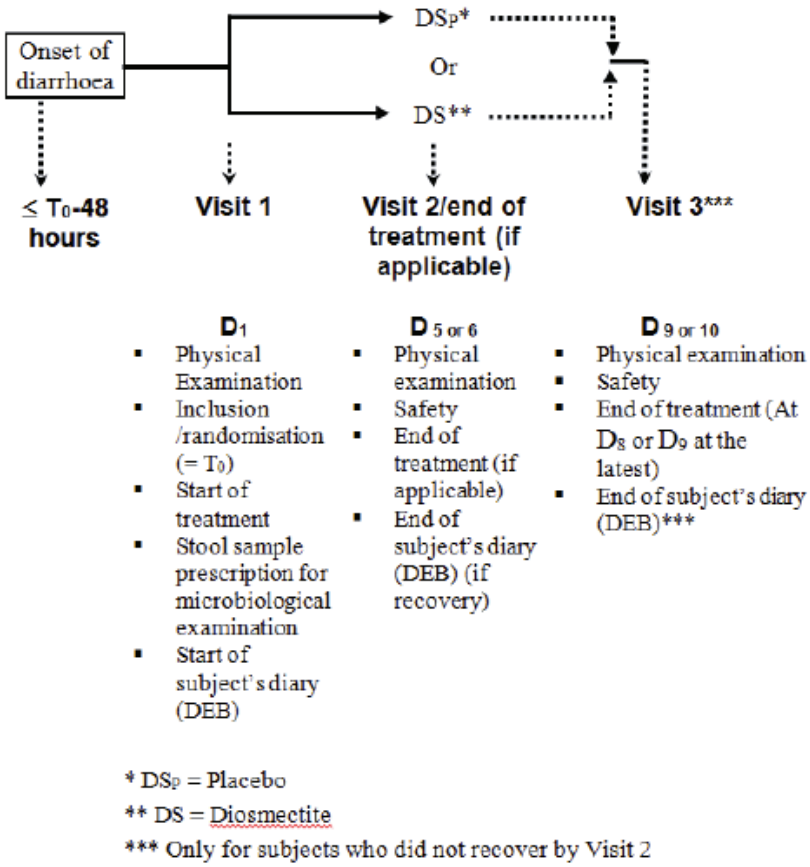
The study is a multicentre, prospective, double blind, placebo-controlled randomised comparative study. Efficacy and safety of diosmectite (administered at a dose and treatment regimen in line with diosmectite Summary of Product Characteristics (SmPC) for France (the daily dosage can be doubled at the beginning of treatment for acute episode)) will be evaluated in adult subjects with a recent episode of acute diarrhoea presumed of infectious origin.

At Visit 1, subjects will be randomised to 1 of the 2 treatment groups (either diosmectite or placebo). 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 subject 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 subject. 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.

Figure 1: Study Design



1.2.1 Study population

854 subjects will be randomised to one of the two treatment groups (either active or placebo) at a ratio of 1:1 (i.e. 427 per treatment group). It is planned to recruit subjects in 90 centres in 7 countries, including Algeria, Czech Republic, Egypt, Lebanon, Poland, Romania and Tunisia.

1.2.2 Study exposure

The overall duration of the study will be approximately 34 months:

- Expected recruitment duration: 34 months.
- Expected subject participation duration: 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).

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

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.

Following confirmation of eligibility for the study, subjects will be allocated to either diosmectite or placebo. The investigator will under no circumstances change the randomisation number and the treatment arm allocated to the subject.

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

The Diary Evaluation Booklet (DEB):

The primary endpoint 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), presence of symptoms such as nausea, vomiting, abdominal pain, anal irritation, and study drug consumption (number of sachets taken each day).

The Bristol scale:

The Bristol stool scale is designed to classify the form of human faeces into seven categories as follows:

- 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 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).

Abdominal Pain intensity:

Abdominal pain intensity, using a 5-point ordinal scale, will be recorded by the subject in the DEB, per 12-hour period. In case of absence of abdominal pain, subject will tick "no" and in case of presence, subject will tick yes and then level of pain be rated as follows: 1= mild, 2 =moderate, 3 = severe, 4= very severe.

Presence of associated diarrhoea symptoms:

Associated symptoms such as nausea, vomiting, abdominal pain and anal irritation, will be recorded by the subject (by ticking yes or no), per 12-hour period (except on Day 1, depending on whether first two sachets were taken before or after noon), in the DEB.

1.3.2.2 Safety assessments

Adverse Events (AEs)

AEs 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

Physical Examination

Physical examinations, including body weight (kg) and body height (cm), will be conducted at Baseline (Visit 1), at Visit 2 and at Visit 3 if applicable. Height will be measured at Baseline only.

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.

Vital Signs

Blood pressure (mmHG) and heart rate (bpm) will be recorded after five minutes rest in sitting position at baseline (Visit 1) and each post-baseline visit, as well as body temperature (in °C using an oral/rectal/axillary/auricular/forehead/temporal thermometer).

1.3.2.3 Other assessments

Demographic data (date of birth and sex), medical and surgical history, including ongoing medical conditions, prior medications for acute diarrhoea episode as well as other prior medications will be collected at first visit.

A history of current acute diarrhoea episode will also be recorded, including:

- Date and time (hours, minutes) of first unformed loose or watery stool,
- Number of stools including number of unformed loose or watery stools, 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.

One faecal sampling for microbiological examination 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:

Virology testing:

- Rotavirus,
- Adenovirus,
- Norovirus.

Bacteriology and parasitology testing:

- Enteropathogenic and Enterotoxigenic Escherichia Coli (E. coli),
- Staphylococcus aureus,
- Shigella,
- Salmonella,
- Campylobacter,
- Yersinia enterocolitica,
- Amoeibiasis (entamoeba histolytica),
- Giardia / lamblia.

1.3.2.4 Withdrawal/discontinuation

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 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.

1.3.3 Schedule of assessments

Table 1 Schedule of Assessments

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

1.3.4 Planned sample size

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 [1]), 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% of subjects prematurely withdrawn without recovery and a maximum of 10% of non-evaluable subjects (because of poor/incomplete diary completion). Accordingly, 854 subjects (427 per treatment group) will be required in order to achieve an 80% power.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Efficacy

2.1.1 Intention-To-Treat population (ITT)

The ITT population will be defined as all randomised subjects analysed according to the arm to which they were randomised.

2.1.2 Modified Intention-To-Treat population (mITT)

The mITT population will be defined as 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.

*The efficacy assessment will be based on the DEB. Therefore subjects with DEB where primary endpoint cannot be derived will be excluded from the efficacy analysis. Any exclusion from efficacy analysis should be discussed and finalized during the Data Review Meeting.

2.1.3 Per Protocol population (PP)

The Per Protocol population will be defined as all subjects in the mITT population for whom no major protocol violations/deviations occurred.

Criteria for exclusion from the Per Protocol population should be provided in the Protocol Deviation Plan and detailed in the Protocol deviations Specifications

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.

2.2 Safety

The safety population will be defined as all randomised subjects with at least one dose of study medication analysed according to the actual treatment received.

2.3 Other populations

2.3.1 Screened population

The screened population will be defined as all subjects enrolled who provided their written informed consent.

2.4 Pharmacokinetics

Not applicable.

2.5 Primary population

The primary analysis based on the primary efficacy endpoint 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, if at least 10% of the subjects in the ITT set are excluded from the PP set, analysis will be performed on the PP population as secondary.

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

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guidelines and will be based on the pooled data from the individual study sites, unless otherwise stated.

BIOTRIAL will perform the statistical analysis of this study under the supervision of the Medical affairs Biometry department of IPSEN.

3.1.1 Primary efficacy endpoint(s)

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.

3.1.2 Secondary efficacy endpoint(s)

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 per eCRF to recovery defined as first formed stool followed by a nonwatery stool, recorded in the DEB

(c) Time (hours, minutes) from diarrhoea onset recorded in the eCRF 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.

3.1.3 Safety endpoint(s)

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.

3.1.4 Multiplicity

No adjustments for multiple testing are planned. Only primary analysis of the primary endpoint (ITT population) will be considered confirmatory.

3.1.5 Significance testing and estimation

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.

3.2 Analysis methods

3.2.1 Efficacy

3.2.1.1 Primary efficacy analysis

(a) Main analysis

The primary analysis of efficacy data will be performed on the ITT population.

The primary endpoint (time from the first study treatment intake (T0)) to recovery defined as 1st formed stool followed by a nonwatery stool (in hours), will be analysed using a time to event methodology.

Any stool recorded before dosing should not be taken into account in the analysis.

The time to recovery will be given in hours and will be analyzed using the Kaplan Meier (KM) survival analysis method (see SAS syntax hereafter). The median recovery time, first and third quartiles with their 95% CIs will be estimated for each treatment group using KM product-limit estimation. In addition, KM cumulative estimators will be computed for recovery rates at 12, 24, 36, 48, 60, 72, 84, 96 hours and estimates for every 12 hours thereafter as applicable.

Results will be also presented graphically in Kaplan-Meier plots.

The primary analysis will test the equality of time to recovery between the two treatment groups, applying the two-sided Gehan-Wilcoxon test (α =5%) based on the ITT set.

The following Null-hypothesis is tested:

$$H_0: \lambda A(t) = \lambda B(t) \text{ versus } H_1: \lambda A(t) \neq \lambda B(t),$$

where $\lambda(t)$ represents the hazard at time t, A=diosmectite and B=placebo.

CCI [redacted]

Subjects prematurely withdrawn without recovery or ending the study without recovery will be censored (not responder) at their last date/time of stools as recorded in the DEB.

Special cases of censoring: subjects who have not filled in the DEB (i.e. no post baseline evaluation regarding "stool number" and "consistency" according to Bristol scale) will be censored at the date and time of their first study drug intake (or the randomisation date time if not administered).

A frequency table of reasons of censoring will be displayed by treatment group.

Rules for handling incomplete dates and times recorded on the DEB are described in section 3.2.3.2.

(b) Secondary analysis

Additionally, for the main efficacy variable, a supportive analysis using mITT and PP populations will be carried out.

(c) Sensitivity analysis – Adjustment by Country

Sensitivity analyses will be conducted to further explore the primary efficacy endpoint adjusting by country, on the ITT set, using the SAS syntax below:

CCI [redacted]

Subgroup analysis:

- Kaplan Meier estimates will be displayed graphically by country if the sample size of each country is sufficient (at least 15 subjects for each country per treatment group).
- Kaplan Meier estimates (median and 95%CI) will also be presented in tables by treatment group as well as the Hazard Ratio (HR) (including 95%CI) of diosmectite over placebo calculated by means of Cox hazard model (see SAS syntax below):

CCI [redacted]

- Hazard ratios including 95% CIs of all subgroups will be presented in a forest plot.

These analyses will be purely explorative and no adjustment for multiplicity will be performed.

(d) Sensitivity analyses – patients with positive parasitology testing.

Patients with positive parasitology testing (i.e. with amoeibiasis or giardia/lamblia) could have gastro- enteritis corresponding to the protocol inclusion criteria and therefore be included in the study, considering the investigator is not aware of these pathologies. Since diosmectite is known to have no efficacy on the diarrhoea linked with amoeibiasis or giardia/lamblia, these patients will have to be handled differently for the analysis.

- If there are few patients with positive parasitology testing (<30): a sensibility analysis excluding these patients will be performed. Therefore, the same analysis as primary analysis will be performed on the subgroup of patients without these pathologies, based on ITT population.
- If the number of patients with positive parasitology testing is important (>=30): the Kaplan-Meier analysis will be adjusted with the parasitology factor (same analysis as for country adjustment described in paragraph (c)). Additionally, the analysis will be performed for each subgroup.

(e) Sensitivity analyses – patients with positive bacteriology testing.

The same sensibility analysis will be performed for patients with a positive bacteriology testing (i.e. with Enteropathogenic or enterotoxigenic E. Coli, Staphylococcus aureus, Shigella, Salmonella, Campylobacter or Yersinia enterocolitica).

(f) Sensitivity analysis – recovered patients without recovery confirmation.

For patients whose last stool is a formed stool without any other subsequent stool to allow the confirmation of the recovery will be considered having recovered. This new endpoint will be analysed using the same methodology as for the primary efficacy endpoint on the ITT set.

(g) Baseline prognostic factors

The same subgroup analysis will be performed for the following baseline variables: Season of randomisation, Absence/Presence of faecal pathogens (virology, bacteriology and parasitology testing), Time since diarrhoea onset.

Cox analyses to assess the impact of baseline prognostic factors

A multivariate analysis of the time-to-recovery will be performed in order to take into account prognostic factors. A Cox proportional hazards model [2] will be performed to estimate the HR and its two-sided 95% CI.

The factors included in this analysis will include but will not be limited to (see section 3.2.18 for the parameterization):

Table 2 Prognostics factors for the Cox model analysis

Covariate	Categories
Time since diarrhoea onset	≤ median (reference) > median
Number of watery stools during the last 24 hours prior inclusion	Not applicable.
Country	Algeria, Czech Republic, Egypt, Lebanon, Poland, Tunisia (largest country to be used as reference)
Season of randomisation	Winter (reference), Summer.
Absence/presence of faecal pathogens for Virology testing	Positive (Rotavirus or Adenovirus or Norovirus) (reference), Negative (None) Not done/missing
Absence/presence of faecal pathogens for Bacteriology testing	Positive (Enteropathogenic or enterotoxigenic E. Coli or Staphylococcus aureus or Shigella or Salmonella or Campylobacter or Yersinia enterocolitica) (reference) Negative (None) Not done/missing
Absence/presence of faecal pathogens for Parasitology testing	Positive (aemibiasis or Giardia/lamblia) (reference), Negative (None) Not done/missing.

Since it is an exploratory search, other covariates may be added.

Step1:

Each of the potential factors associated with recovery listed in Table 2 together with the treatment variable will be tested in separate Cox proportional hazards models. Any factors found to be significant at $p \leq 0.20$ (via the Wald chi-square test statistic)

will be considered to be potentially important. The association between each covariate and treatment will be further explored by presenting separate KM plots for each level of the covariate.

For this selection, the following SAS® code will be used:

CCI

Step2:

In a second step, each pre-selected parameter will be tested with the other retained parameters at the 0.001 level to confirm that there is no strong link between them. For continuous variables the Pearson correlation will be tested. For a mix of categorical and continuous variables Spearman's correlation coefficient will be used and for categorical variables a Chi2 test will be used. If the independence is not met for two parameters ($p < 0.001$) or $r \geq 0.5$, the choice will be done according to clinical and statistical relevance.

Step3:

All selected parameters will be entered into a multivariate Cox model. The stepwise variable selection method in the SAS® procedure PHREG will be performed with p=0.20 to enter variables in the model, and p=0.15 to remove variables from the model, to select the best model, in addition to the treatment variable which will be included in the model.

Tied events will be handled with the Exact method:

CCI

The interaction of each remaining term in the multivariate model with treatment will also be investigated. This will be done by adding interaction terms to the model. If there is evidence of any interaction with treatment (according to the p-value of the likelihood ratio test statistic obtained with TYPE3(LR) option of MODEL statement), the significant interaction terms (at $p \leq 0.10$) will be maintained in the model.

The maximum likelihood estimates of model coefficients (with associated standard error, degrees of freedom, Wald Chi-square statistic and p-value) will be presented for the final model along with the hazard ratios and 95% confidence intervals.

A single vertical bar graph will be presented showing the hazard ratios and 95% CIs (in favour of diosmectite or Placebo) from the separate individual models (i.e., each model containing a single covariate along with terms for treatment).

The hazard ratio and 95% CI from the overall final multivariate model will also be included in the above mentioned figure. For any covariate where the treatment by

covariate interaction is significant in the final multivariate model, the hazard ratio for treatment within each level of the covariate will be shown.

Then, the assumptions of proportional hazards (PH) will be examined both graphically and statistically.

The graphical methods used will be:

- Plot ln(-ln(S(t))) versus t or ln(t) and look for parallelism
- Plot Observed and predicted S(t) and look for close fit.
- Use the PH graph by using the ASSESS option of the PHREG procedure of SAS®. ASSESS statement in SAS® includes plot of randomly generated residual processes to allow for graphic assessment of the observed residuals in terms of what is "too large": i.e. the path from the actual data is compared to the randomly-generated paths under PH.

  The following SAS® code will be used with the final model retained:

The second method to check the proportional hazards assumption will be using the time-dependent covariates, i.e. time*covariate interactions will be added to the model.

The following SAS® code will be used

The form of the interaction that will give the more efficient estimates (ex: TIME or log (TIME) must be chosen. With log(TIME), TRTPt=TRTP*log(TIME).

If the added interaction is not statistically significant at the level of 0.10, this indicates that proportional hazard assumption is satisfied.

On the contrary, if the interaction is statistically significant, it means that the effect of the given covariate is not constant over time, so PH assumption is violated. To solve this problem (i.e. to model the non-PH), the interaction will be left in the model.

If PH fails for a covariate VARXi, previously checked covariates will be re-check after adjusting for the non-PH of VARXi.

The second method used to handle non-PH will be to enter the covariate VARXi as a stratification variable in the model to have the estimation for each level of the covariate:

CCI [redacted]

Therefore, the model with interaction and stratified model will be run, and the model with best fit statistics will be chosen.

Finally the estimation of the best model (selected with the stepwise procedure) will be presented, as well as the best model adjusted for non-PH, if applicable.

All the SAS outputs produced during the analyses and the model checking procedures will be included in the statistical appendix (see section 4.3).

3.2.1.2 Secondary efficacy analysis

The analysis regarding secondary efficacy endpoints will be performed on the ITT population. Supportive analysis using PP population will be carried out if more than 10% of subjects are excluded from ITT set.

Rules for handling incomplete dates and times recorded on the DEB are described in section 3.2.3.2.

(a) Abdominal pain intensity per 12-hour period

Intensity of abdominal pain per 12-hour period will be summarized by treatment group (an absence of pain will be considered as value zero).

Considering the ordinal nature of the outcome, difference between diosmectite and placebo will be studied by fitting a cumulative logit model assuming an ordered multinomial response distribution. The model will include treatment group as fixed effects and a random intercept effect. Contrasts between diosmectite and placebo will be given in term of odds ratios (modelling the probabilities to obtain higher scores of pain intensity). The model will be performed for each time point (12-hour period) separately (see SAS Syntax below).

CCI [redacted]

(b) Time from diarrhoea onset to recovery

This endpoint is a time to event endpoint which will be analysed using the same methodology as for the primary efficacy endpoint. The date and time of diarrhoea onset will be the start date and time of diarrhoea onset as recorded from the “History

of current acute diarrhoea episode" eCRF section. Subjects will be censored using the same rules as defined for the primary endpoint.

(c) Time from diarrhoea onset to the first formed stool.

This endpoint is a time to event endpoint which will be analysed using the same methodology as for the primary efficacy endpoint.

(d) Time from the 1st study treatment intake to the last watery stool.

This endpoint is a time to event endpoint which will be analysed using the same methodology as for the primary efficacy endpoint.

(e) Number of stools, per 12-hour period.

Number of stools per 12-hour period (0-12h, 12-24h, 24-36h…) will be computed by summing the number of stools as recorded in the DEB by the subject using the time (24-hour clock) of visit to restrooms. The number of stools per 12-hour period will then summarized by treatment group. From first to last intake, if no stool is reported in the diary at a specific time interval, the number of stools at the considered 12-hour period will be considered as zero.

Any stool with a missing evaluation consistency should be counted in the total number of stools per 12-hour period (if time of stool is not missing).

Any stool with a missing time, with a consistency evaluation and which is embedded within the same time interval will be counted in the number of stools for the considered time interval. The number of stools per 12-hour period during the post baseline period will be analysed with an analysis of covariance (ANCOVA) method with repeated measurements. The model will include number of stools 24 hours before randomisation (baseline) as covariate, treatment, time point (12-hour period until visit 3), the treatment by time point interaction as fixed effects and subject as random effect. The residual variance-covariance pattern will be fitted using an unstructured matrix (see SAS Syntax below). Adjusted means, 95% CIs and corresponding p-values of differences between diosmectite and placebo, derived from the model, will be displayed globally and for each time point.

CCI

If the model fails to converge, only time intervals with a sufficient number of patients could be included in the model.

In the event of gross violations from the normality assumptions (identified using the shape of the distribution and QQ plots of change from baseline overall and by visit) or from the covariance model assumptions or in case of convergence criterion fails to be reached, a non-parametric analysis will be used instead (Mann-Wilcoxon-Mann-Whitney test (see SAS syntax below)) at each time point separately.

CCI [redacted]

In addition the cumulative number of stools per 12-hour period will be presented graphically using barcharts of means (± SEM) on observed values at each time point by treatment group.

(f) Number of watery stools, per 12-hour period.

The same analysis as described above will be performed for number of watery stools (corresponding to type 6 or 7). 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.

(g) Percentage of subjects with associated symptoms such as nausea, vomiting, abdominal pain and anal irritation, per 12-hour period.

The proportion of subjects with at least one associated symptom will be displayed per treatment group and per 12-hour period, using data retrieved from the DEB for post baseline values and using data retrieved from the eCRF for baseline value (Presence of associated symptoms during the last 24 hours from the "History of current acute diarrhoea episode" page). Same results will be displayed for each symptom separately: nausea, vomiting, abdominal pain and anal irritation. To assess the treatment effect at each 12-hour period on associated symptoms overall and on each symptom separately, a non-linear mixed model will be used including treatment and status of subjects at baseline (With or without associated symptoms), time-point and treatment by time-point interaction as fixed effects and number of watery stools during 24h prior inclusion as covariate (see SAS Syntax below).

CCI [redacted]

In addition the percentage of subjects (with at least associated symptom and for each symptom separately) per 12-hour period will be presented graphically using barcharts at each time point by treatment group.

3.2.2 Safety

All safety data will be included in the data listings and summary tables will be based on the safety population.

3.2.2.1 Adverse events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.0.

Listings will be presented and sorted by treatment group, subject id, start time of AEs, primary system organ class, preferred term and verbatim text for all adverse events recorded during the study.

Listings of serious adverse events (SAE), adverse events leading to withdrawal and listings of deaths will also be presented.

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. A TEAE is defined as any AE that occurs during the active phase of the study (i.e. from the first study drug intake until 48h after last study drug intake) and 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 Adverse Events (TEAE) will be flagged (*) in the adverse events listing and will be summarised.

Related adverse events are those events with causality missing or related.

An overall summary table of all AEs with the number and percentage of subjects with at least one:

- AE,
- TEAE,
- TEAE by intensity,
- TEAE by causality,
- TEAE by intensity and causality,
- SAE,
- TEAE leading to premature withdrawal of study.

Note: In the event of multiple adverse events (corresponding to different PTs) being reported by the same subject, each subject is counted for each intensity level, each causality level or each intensity and causality combined level. That means that the total of subjects for all levels of intensity / causality might be higher than the overall number of subjects with at least one AE.

Incidence of all reported AEs, TEAEs, SAEs and non-serious AES (classified by primary System Organ Class (SOC) and Preferred Term (PT)) will be tabulated by treatment group. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs/SAEs associated with premature withdrawal of study.

Note: In the event of multiple occurrence of a same AE (same Preferred Term) by the same subject, the maximum intensity (severe > missing > moderate > mild) and the most serious causality (related > not related) will be chosen.

Note: In case of missing data for relationship/intensity, the AE (PT) will be presented with the most severe category (related and/or severe) when crossing intensity and relationship.

3.2.2.2 Laboratory data

Not applicable.

3.2.2.3 Vital signs

Vital signs will be listed at each assessment by treatment group and subject. Any unscheduled vital signs will be flagged [U] in the listing.

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

Summary statistics by treatment group will be presented (blood pressure, heart rate in sitting position, body temperature and body weight) at each scheduled assessment for actual values and changes from baseline.

3.2.2.4 ECG

Not applicable.

3.2.2.5 Other assessments (as applicable)

Any new or worsening clinically significant abnormal physical examination results should be recorded on the Adverse Event eCRF page and will be part of the AE analysis.

3.2.3 Missing data and outliers

3.2.3.1 Missing data

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

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

3.2.3.2 Missing or incomplete dates

Missing date and/or time related to stools in patients diaries for time-to-event analyses (time to recovery, time to first formed stool, time to last watery stool, time to recovery without confirmation):

Rules of imputation for events: in case of time information is missing but information on date and on stool consistency are available, the time will be imputed:

- to 23:59 if there is no other subsequent stools the same day,
- to time of the next stool the same day minus 1 minute otherwise.

Rules of imputation for censoring: in case of time information is missing but information on date and on stool consistency are available, the time will be imputed:

- to the half of the interval (i.e. to (24:00 - time of last stool) / 2) if there is at least one non-missing time the last day
- to 12:00 a.m. if there is no other available times the last day

Missing first administration time for time-to-event analyses:

If time of first administration is missing for a subject, it will be imputed with the date/time of the first stool after randomization as recorded in the diary. If date/time of randomization is also missing, time of first intake will be imputed with the time of the first stool of the diary.

Other:

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

(1) The most conservative approach will be systematically considered (i.e. if the onset date of an AE/concomitant medication is missing / incomplete, it is assumed to have occurred during the study treatment phase (i.e. a TEAE for AEs) except if the partial onset date or other data [stop date, …] indicates differently).

(2) A missing/incomplete date of medical history or disease diagnosis will be assumed to have occurred before any study treatment.

(3) If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (i.e.: an AE could be assigned to several possible doses at event onset according to its partial onset date and stop date. Particularly an AE with missing start date will be assigned to each dose received before its end date. Similarly a medication with partial start and stop dates could be considered as prior and concomitant treatment).

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

3.2.3.3 Outliers

Any outlier identified prior to unblinding which is impossible/unplausable will be excluded from the analysis. For other identified outliers, the impact should be assessed by performing the statistical analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect.

If any outliers are identified after unblinding the statistical analysis should be performed with the actual values and at least one other analysis eliminating or reducing the outlier effect.

A search of outliers/missing values by BIOTRIAL should be performed before the unblinding and actions with the sponsor should be defined. This will be done for variables used for the primary and secondary analysis. A specific focus will be on the DEB data and especially on the dates and times of each recorded stool (missing values and chronological order) and their consistencies including summaries of number of stools overall and according to Bristol scale). The date/time of first watery stool (i.e. diarrhoea onset) recorded on the eCRF will also be examined (if time missing) as well as the number of stools and watery stools during the last 24

hours period (baseline data). A detection of abnormal values for raw and changes from baseline on vital signs data will also be performed.

3.2.4 Subject disposition

A listing of dates of assessments (relative day) and their study exposure will be presented by subject for each treatment group. A summary table will present the extent of subject exposure in the study for each treatment group.

The numbers and percentages of subjects in each of the ITT, mITT, PP and safety 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 randomized, treated, discontinued and completed will be tabulated by treatment group. Primary reasons for discontinuation of study will be tabulated.

All the protocol deviations identified prior to unblinding will be listed by subject for each treatment group.

3.2.5 Withdrawals

Discontinued subjects will be listed and a summary table of the number and percentage of subjects who withdrew from the study and the reasons for withdrawal will be presented by treatment group.

3.2.6 Demographic and baseline characteristics

Baseline value will be defined as the value measured at first visit and if missing, the last evaluable value before the first administration of study drug if any.

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

Summary statistics will be provided for demographic and baseline characteristics by treatment group, for the ITT population.

3.2.6.1 Demographics data

Demographic characteristics will be summarized using the following information:

- Age (years): summary statistics.
- Gender: number (%) of subjects for Male/Female.
- Country: number (%) for Algeria, Czech Republic, Egypt, Lebanon, Poland, and Tunisia.
- Body Height (cm): summary statistics.
- Body Weight (kg): summary statistics.
- BMI (kg/m^2): summary statistics and number (%) for the following categories: Underweight ($< 18.5\ kg/m^2$), Normal or Healthy Weight ($[18.5 – 25.0[\ kg/m^2$), Overweight ($[25.0 – 30.0[\ kg/m^2$) and Obese ($\geq 30.0\ kg/m^2$).
- Seasons of randomisation (according to date of randomisation): number (%) of subjects in each category: winter and summer.
- Virology, Bacteriology and Parasitology testing: number (%) of subjects for Positive/Negative/Not done or Missing.
- Time since diarrhoea onset: number (%) in category ≤median and > median

3.2.6.2 Other Baseline characteristics

- History of disease: diarrhoea episode characteristics will be summarized using the following information from the "History of current acute diarrhoea episode" eCRF page:
  - Duration since diarrhoea diagnosis (hours): summary statistics
  - Time since diarrhoea onset: number (%) in categories [0-12H[; [12-24H[; [24-36H[; [36-48H[; ≥48H.
  - Number of stools during the last 24 hours: summary statistics on overall and for:
    - Stools/unformed loose or watery stools of the first 12 hours-period
    - Stools/ unformed loose or watery stools of the second 12 hours-period
  - Presence of associated symptoms during the last 24 hours: number (%) of subjects in each category Nausea (Yes/No), Vomiting (Yes/No), Abdominal pain (Yes/No), Anal irritation (Yes/No).
- Results of virology/microbiology for stool examination:
  - Results of Virology testing with number (%) of subjects in each category: Rotavirus, Adenovirus, Norovirus, None, Missing.
  - Results of Bacteriology and parasitology testing with number (%) of subjects in each category:
    - Bacteriology subgroups: Enteropathogenic and enterotoxigenic E. Coli, Staphylococcus aureus, Shigella, Salmonella, Campylobacter, Yersinia enterocolitica, None, Missing.
    - Parasitology subgroups: Aemibiasis (entamoeba histolytica), Giardia/lamblia, None, Missing.
  - Additionally, above frequency tables will be provided with number (%) of patients with a positive result to:
    - Virology and parasitology,
    - Virology and bacteriology,
    - Parasitology and bacteriology,
    - Virology, bacteriology and parasitology.

3.2.7 Medical and surgical history, Non-Drug therapies, concomitant surgical procedures

Medical and surgical history will be coded using MedDRA Version 22.0 as well as Prior and Concomitant Non-Drug therapies and Concomitant Surgical Procedures.

Listings will present the preferred term and verbatim text. The listings will be sorted by treatment group, subject, primary system organ class, preferred term and verbatim text.

Frequency tables of the number and percentage of subjects will be provided by primary system organ class and preferred term for each treatment group for:

- Prior medical and surgical history: separately for prior and ongoing conditions
- Concomitant non-drug therapy
- Concomitant surgery.

Prior non-drug therapies will only be listed.

In the event of multiple incidences of the same primary system organ class /preferred term being reported by the same subject, the subject will be counted once for that primary system organ class/preferred term.

These summaries will be produced on the safety population.

3.2.8 Subject compliance

Data collected from both "Study Treatment Administration (on site)" eCRF section and "Study drug intake" part of the DEB will be presented in individual listings with information such as date of intake, time of intake when taken on site and number of sachets taken by the subject. Listings will be ordered by treatment group, subject and visit, for all subjects of the Safety set.

Study drug exposure (days) will be summarized on the safety population.

Summary statistics on number of sachets taken during the mandatory period (from Day1 to Day4/Day5), until recovery and until end of study will be displayed by treatment group.

Compliance will be expressed in percentage as the total sachets taken based on the expected total sachets to be taken and will be calculated during the mandatory treatment period for all subjects, until the recovery for subjects with recovery and until the end of study for subjects with no recovery (see section 3.2.12). Compliance will be categorized as < 80% (Under compliance), 80-120% (Compliance) and > 120% (Over compliance) and will be summarized in percentage and in class overall, on the safety population.

3.2.9 Prior and concomitant therapies

Two types of medications will be analysed:

- **General medications:** using the information retrieved from the "Prior and Concomitant Medications (Excluding current acute diarrhoea episode)" eCRF section.
- **Medications related to current diarrhoea episode**: using the information retrieved from the "Prior and Concomitant Medications for the current acute diarrhoea episode" eCRF page.

Prior medications are defined as the medications taken within 30 days preceding visit 1 and stopped prior to the first study drug intake.

Concomitant medications are defined as medications that have been taken during the treatment period regardless the start or stop date. For any partial date, if it is not clear when the medication started or ended but shows a possibility that it has been taken during the treatment period then it will be considered as a concomitant medication.

All therapies will be coded using the latest version of WHO-Drug Dictionary. The therapeutic class will correspond to the second level of ATC code, that is, corresponding to the first 3 figures (see section 3.2.12-Derived data).

Listings will be presented for the therapeutic class, preferred term and verbatim text. The listings will be sorted by treatment group, subject, chronological start date, therapeutic class, preferred name and verbatim name.

Frequency tables of the number and percentage of subjects in the safety population for each treatment group and on overall, by therapeutic class and preferred name will be provided:

- for general prior and concomitant therapies,
- for prior and concomitant therapies for acute diarrhoea.

3.2.10 Pharmacokinetics & antibodies (if applicable)

Not applicable.

3.2.11 Pharmacodynamics (if applicable)

Not applicable.

3.2.12 Derived data

The derived data are variables which are calculated from the raw data in the eCRF or DEB data and not included in the database.

Efficacy derived variables:

Primary endpoint:

- 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):

  (Date/time of Recovery or last date/time of stool (if censored) – date/time of 1st treatment intake).

  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). Dates and times will be retrieved from the DEB filled in by the subject. Imputations rules in case of partial time variables are described in section 3.2.3.2. Stools without consistency evaluation will not be taken into account for the determination of recovery.

  Rules of censoring are described in the table below:

Event	Decision	Date of event or censoring to consider for the analysis
Recovery	Not censored	Date/time of first form stool followed by a nonwatery stool
No recovery and subject completed the study	Censored	Date/time of last stool
No recovery and subject prematurely withdrawn the study	Censored	Date/time of last stool

Event	Decision	Date of event or censoring to consider for the analysis
No recovery and no post-baseline evaluation of stools	Censored	Date/time of first IMP intake (if administered)
		Date/time of randomisation (if not administered)

Secondary endpoints:

- Time from diarrhoea onset to recovery (hours) will be calculated as follows:

  (Date/time of Recovery or last date/time of stool (if censored) – date/time of diarrhoea onset).

  The date and time of diarrhoea onset will be the start date/time of first unformed loose or watery stool as recorded in the "History of current acute diarrhoea episode" eCRF page.

  Rules of censoring are the same as described for primary endpoint.

- Time from diarrhoea onset to the first formed stool (hours) will be calculated as follows:

  (Date/time of 1st formed stool or last date/time of stool (if no formed stool) – date/time of diarrhoea onset).

  The date of 1st formed stool will be the earliest date of stools with a formed consistency corresponding to type 1 to 4, whatever the consistencies of the next stools.

  Rules of censoring are described in the table below:

Event	Decision	Date of event or censoring to consider for the analysis
Formed stool	Not censored	Earliest Date/time of formed stool
No formed stool and subject completed the study	Censored	Date/time of last stool
No formed stool and subject prematurely withdrawn the study	Censored	Date/time of last stool
No formed stool and no post-baseline evaluation of stools	Censored	Date/time of first IMP intake (if administered)
		Date/time of randomisation (if not administered)

- Time from the first study treatment intake to the last watery stool (hours) will be calculated as follows:

  (Date/time of last watery stool or last date/time of stool (if censored) – date/time of 1st treatment intake).

  The date of last watery stool will be the latest date of stools recorded by the subject, with a consistency corresponding to type 6 or 7.

  Rules of censoring are described in the table below:

Event	Decision	Date of event or censoring to consider for the analysis
Watery stool	Not censored	Date/time of last watery stool

Event	Decision	Date of event or censoring to consider for the analysis
No watery stool and subject completed the study	Censored	Date/time of last stool
No watery stool and subject prematurely withdrawn the study	Censored	Date/time of last stool
No watery stool and no post-baseline evaluation of stools	Censored	Date/time of first IMP intake (if administered)
		Date/time of randomisation (if not administered)

- 12-hour period (for analysis of number of stools and number of watery stools): is defined as the number of hours between the date/time of stool recorded in the DEB and the date/time of first IMP intake and will be expressed in time intervals of 12 hours ([0-12h[, [12-24h[, [24-36h[….).

Other derived variables

The following derived data will be calculated and included in the listings:

- **Study day**

Study day based on the 1st treatment intake will be calculated as following:

If the date was on or after treatment intake then

Study day = Date - date of study treatment intake + 1

If the date was before treatment intake then

Study day = Date - date of study treatment intake.

- **Study exposure (days)**

Study exposure (days) will be calculated as follows:

Exposure (days) = (Date of Last Study Visit – Date of Informed Consent + 1).

- **Study Drug Exposure (days)**

Drug exposure (days) = (last sachet intake date – first sachet intake date + 1).

- **Compliance (%)**

Compliance of study medication will be calculated as follows:
Compliance (%) = (Total sachets taken / Expected total sachets) x 100.

(a) During the mandatory treatment period:

Expected total sachets = 24 therefore,
Compliance = (Total sachets taken from Day1 to Day4 or Day5) / 24.
The number of sachets taken by the patient during the mandatory period will be derived according to the time of day at which the subjects has taken the first of two sachets on day 1: in the morning if the first two sachets have been taken before 11:00 a.m. (<11:00 a.m.), the afternoon if taken between 11:00 a.m. and 6:00 p.m. ([11:00 a.m.; 6:00 p.m.]) and the evening if taken after 6:00 p.m. (>6:00 p.m). Patients with a missing time of first administration will be considered to have taken their first two sachets in the morning (i.e. before 11:00 a.m.).

(b) Until recovery for subjects with recovery:

Expected total sachets will be calculated using date and time of recovery according to diary:

Expected total sachets = (Date of confirmation of Recovery – Date of 1st sachet intake +1) * 6([1]) ([2]).

([1]): the expected number of sachets for each day is theoretically 6 sachets. For the day of recovery, according to the time of last nonwatery stool which immediately follows the recovery (confirmation of recovery), the theoretical number of sachets will be: 0 sachet if time of the last nonwatery stool is before 07:00 a.m. (<7:00 a.m) (i.e. the subject is considered to have taken no sachet the day of recovery), 2 sachets if time of last nonwatery stool is between 7:00 a.m. and 12:00 p.m. ([7:00 a.m.;12:00 p.m.[), 4 sachets if time of last nonwatery stool is between 12:00 p.m. and 7:00 p.m. ([12:00 p.m.;7:00 p.m.] and 6 sachets if time is over 7:00 p.m. (>7:00 p.m).

In case of missing data, the time of confirmation of recovery will be imputed as follows:

- if the day of confirmation is the same as the day of recovery, time of confirmation will be imputed by the time of recovery +1 minute
- if the day of confirmation is not the same, date and time of confirmation will be imputed by the day of confirmation and time to 00:01 a.m.

([2]): the number of expected sachets to be taken on the first day of intake will depend on the time of the first intake. If the first sachets were taken after noon by the subject, 2 sachets will be subtracted from the total expected number of sachets for that subject at day 1.

If the recovery occurs the day corresponding to the first IMP intake, the total expected sachets will be the minimum between the theoretical number of sachets estimated using the time of recovery as described in (1) and using the time of the first IMP as described in (2).

The number of sachets taken by the subject the day of the recovery will be calculated using the time of the confirmation of the recovery only if the number of sachets taken that day is more or equal 6: the subject is considered to have taken 0 sachet if this time is before 7:00 a.m. (<7:00 a.m), 2 sachets is this time is between 7:00 a.m. and 12:00 p.m. ([7:00 a.m.;12:00 p.m.[) and 4 sachets if this time is between 12:00 p.m. and 7:00 p.m. ([12:00 p.m.;7:00 p.m.]. If subject took less than 6 sachets the day of the recovery, the number of sachets taken by the subject is equal to the number of sachets as declared in the diary.

(c) Until the end of study for subjects without recovery:

For the calculation of the compliance, the expected total sachets will be based according to the last visit date of the subject:

For the first day, the number of expected total sachets taken will depend on the time of day at which the subject has taken the first two sachets (cf. rules described in paragraph a). For the subsequent days, the theoretical number of sachets will be 6 by diary day until the last day of the diary, plus:

- 2 sachets if the subject declared to have taken any sachet the last day in the diary (or information is missing in the diary)

- the number of sachets taken by the subject that day if the subject took at least one sachet the last day.

In case of premature withdrawal, if date of collection or date of withdrawal is completed, then the expected total sachets to be taken by the subject will be based on the last available date in the diary.

If patient ended the study on the day of first administration then the expected total sachets will be the minimum between expected sachets according to the time of first administration as described in (a) and the number of sachets taken by the patient that day.

The number of sachets recorded in the DEB on Day 1 ("Study Drug intake" section) includes the first 2 sachets taken on site.

Compliances for patients without diary or with no information on their diary regarding the number of sachets will not be calculated.

- **Change from baseline**

Change from baseline at a given visit will be calculated as a difference from baseline (assessment at the first visit).

- **Therapeutic Class**

The therapeutic class will correspond to the first 3 figures of the ATC code. The decoding of the therapeutic class will be done from the latest version of WHO-Drug Dictionary.

- **Age**

Age (years) will be calculated as follows and truncated to the largest integer that is less than or equal to the calculated result:

Age = (date of first Visit - birth date + 1)/365.25.

- **BMI**

BMI (kg/m^2) at Baseline will be derived as Weight (kg)/[Height(cm)/100]^2 measured at first visit and rounded to the nearest decimal.

- **Season of randomisation**

Season of randomisation will be derived from the month of the randomisation date as follows:

- Summer: if month (randomisation date) is from April to October inclusive,
- Winter: if month (randomisation date) is from November to March inclusive).

- **Duration since diagnosis of current acute diarrhoea**

Duration since current diarrhoea diagnosis (in hours) will be defined using the date/time of diarrhoea onset as recorded in the "History of current acute diarrhoea episode" eCRF page:

Duration (hours) = (date/time of randomisation – date/time of diarrhoea onset).

- **AE duration**

If the start and end dates of the AE are identical then "<1" day will be presented. If the duration is greater than 24 hours then it will be calculated as (end date - start date) +1 and presented in days. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥ (last attended visit date – start date)+1" day(s). If the start date or the end date are

partial the duration will be presented as a superior inequality "≥xx" day(s) (i.e., ≥2 where start date = 31 January 2004 and end date = February 2004 or start date = January 2004 and end date = 01 February 2004].

- **Time since last treatment intake for adverse event**

If the start date of the adverse event is identical to the date of last administration intake, then"<1" day will be presented. If the time to onset is greater than 24 hours then it will be calculated as (start date – last treatment intake date) +1 and presented in days.

If the start date is partial, the time since 1st treatment intake will be presented as a superior inequality (i.e., for an AE started in February 2004 after the last treatment intake performed on 31 January 2004, the time since last treatment intake will be as "≥2" days). If the start date is missing the time since last treatment intake will not be presented.

- **Concomitant therapy duration:**

The duration of concomitant treatments will be calculated as (end date – start date) + 1. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥ (last attended visit date – start date)+1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥ xx" day(s) (i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004) but if both are partial or one is missing, the duration will not be presented.

- **Medical and surgical history duration**

The duration of medical and surgical history will be calculated as (end date – start date) + 1. If the recorded end date is CONT. (for continuing), the end date will be listed as "ongoing" and the duration will be approximated as "≥ (visit 1 day 1 date – start date)+1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥ xx"day(s) (i.e. ≥2 where start date=31JAN2004 and end date=FEB2004 or start date=JAN2004 and end date=01FEB2004) but if both are partial or one is missing the duration will not be presented.

3.2.13 Visit windows (optional)

All data will be organised and analysed according to the scheduled visits outlined in the protocol. As defined by the protocol, visit 1 (baseline visit) has to be performed within 48 hours after onset of diarrhoea. Visit 2 will correspond to Day 5 or Day 6 and Visit 3 (if any) will correspond to Day 9 or Day10.

3.2.14 Rules and data formats

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

For summary statistics, the following will be presented n, number of missing values, arithmetic mean, standard deviation, median and the range (minimum, maximum).

Mean, median, standard deviation and standard errors of the mean (SE) values will be reported to one decimal place greater than the raw/derived data that they summarise. Minimum and maximum values will be reported with the same precision as the raw data.

Percentages will be reported to one decimal place and 0% will not be presented. Percentages will be calculated using a denominator of all subjects in a specified population. Missing values will not be accounted for in denominator. The denominator will be specified in a footnote to the tables for clarification if necessary.

Lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).

Percentiles (e.g., 25%, 75%) should be presented to one decimal place more than the raw/derived data.

Time-to-event endpoints will be descriptively summarized using Kaplan-Meier (KM) product-limit estimators.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

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

3.2.15 Pooling of Centres

Regarding the primary endpoint, it is planned to assess and adjust the treatment comparison by computing the median of time to recovery for diosmectite and placebo for each country (subgroups analysis).

Subjects are planned to be recruited in seven countries: Algeria, Czech Republic, Egypt, Lebanon, Poland, Romania and Tunisia.

3.2.16 Interim analysis

No interim analysis will be performed.

3.2.17 Role of independent data monitoring committee (DMC)/interim data review committee [if applicable]

No independent data monitoring committee/interim data review committee will be used in this study.

3.2.18 Covariates and analysis of subgroups

Subgroups analyses on the primary endpoint are planned for the following group of variables:

Time since diarrhoea onset

- ≤ median (reference)
- > median

Country (largest country to be used as reference)

- Algeria
- Czech Republic,

- Poland,
- Tunisia
- Egypt
- Lebanon

Season of randomisation:

- Winter (reference)
- Summer

Virology subgroup:

- Positive (reference): at least Presence of one of the following:

(a) Adenovirus ,
(b) Rotavirus,
(c) Norovirus,

- Negative: no presence and at least one absence among all above tests
- Not done or missing result for all tests.

Bacteriology subgroup:

- Positive (reference): at least Presence of one of the following:

(a) Enteropathogenic or enterotoxigenic E. Coli
(b) Staphylococcus aureus,
(c) Shigella,
(d) Salmonella,
(e) Campylobacter,
(f) Yersinia enterocolitica,

- Negative: no presence and at least one absence among all above tests
- Not Done or missing result for all tests.

Parasitology subgroup:

- Positive (reference): at least Presence of one of the following:

(a) Aemibiasis (entamoeba histolytica)
(b) Giardia/lamblia

- Negative: no presence and at least one absence among all above tests
- Not done or missing result for all tests.

Covariables used in mixed models will be:

- Number of stools 24 hours before randomisation (baseline) as recorded in the "History of current acute diarrhoea episode" eCRF page and calculated as follows: Number of stools during the first 12-hour period + Number of stools during the second 12-hour period.
- Number of watery stools 24 hours before randomisation (baseline) calculated as follows: Number of watery stools during the first 12-hour period + Number of watery stools during the second 12-hour period.

Missing values will not be replaced.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

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

4.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS version 9.3 or higher. All outputs will be provided as individual.rtf files following GEN014 template and compiled in bookmarked .pdf files as per ICH section (e.g. 14.1, 14.2 …).

4.3 Validation programs

BIOTRIAL will provide a Validation Plan to IPSEN identifying the methods of validation and quality control (QC).

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

The Reviewing/QC Statistician is responsible for checking and reviewing the work produced using whatever method he/she feels is appropriate (e.g., SAS code review, hand calculation, etc.) to reassure of the quality of the output.

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

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

After final review, and when no further changes are required to produce the deliverable, the Program Reviewer and Reviewing/QC Statistician need to complete and sign the CRO's Validation Checklist/Sign-off Sheet, to indicate that they have successfully performed all of their responsibilities.

Copies of the internal QC forms produced for the validation process and the CRO's sign-off forms will be provided to the sponsor to support the validation.

4.4 Restitution of the programs

All programs (including Macros and analysis datasets programs and corresponding datasets) producing the tables, listings and statistical output along with associated logs should be given to the sponsor after each planned delivery (including when the mock TLFs are released).

5 CHANGES FROM PROTOCOL

Not applicable.

6 REFERENCES

1. 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.
2. Cox DR. Regression models and life tables J Roy Statist Soc B. 1972;34:187-220.

7 DATA PRESENTATION

Data listings are presented for all randomized subjects (ITT population) ordered by treatment, subject number and, where applicable, by visit/time-point.

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

The title of each generated table, listing and figure should appear bookmarked within Word (one single bookmark per table/listing/figure) to allow document publishing by IPSEN.