Document Name: dfr00250108-stat-plan

Clinical	Nassima Bekkat 20-Jun-2017 08:10:04 GMT+0000

Clinical	Quyen Nguyen 20-Jun-2017 08:51:40 GMT+0000

Clinical	Tiffany Wang 20-Jun-2017 11:29:53 GMT+0000

Approved

STATISTICAL ANALYSIS PLAN

ASSESSMENT OF ELEMENTAL IMPURITIES LEVEL AFTER CHRONIC ADMINISTRATION OF DIOSMECTITE (SMECTA®) IN SUBJECTS WITH CHRONIC DIARRHEA

PROTOCOL VERSION AND DATE: 4.0 – 07 Sept 2016

SAP Version	Date
Final Version 1.0	20 June 2017

STUDY NUMBER:	D-FR-00250-108
EUDRACT NUMBER	2016-002111-18
PROTOCOL TITLE:	ASSESSMENT OF ELEMENTAL IMPURITIES LEVEL AFTER CHRONIC ADMINISTRATION OF DIOSMECTITE (SMECTA®) IN SUBJECTS WITH CHRONIC DIARRHEA
SAP VERSION:	Final Version 1.0
SAP DATE:	20 June 2017

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

RESPONSIBILITY	NAME, TITLE & OFFICE	SIGNATURE	DATE
Aepodia **Project Manager**	PPD Aepodia S.A.R.L. 3 Avenue du Canada 91940 Les Ulis, France		
Aepodia **Biometry Coordinator**	PPD Aepodia S.A.R.L. 3 Avenue du Canada 91940 Les Ulis, France		
Ipsen **Statistician**	Tiffany Wang Ipsen Innovation 5 Avenue du Canada 91940 Les Ulis, France		
Ipsen **Medical Development Director**	Nassima BEKKAT Ipsen Innovation 5 Avenue du Canada 91940 Les Ulis, France		
Ipsen **PK Director**	Quyen NGUYEN Ipsen Innovation 5 Avenue du Canada 91940 Les Ulis, France		
Ipsen **VP Early Development and Clinical Pharmacology**	Isabelle PATY Ipsen Innovation 5 Avenue du Canada 91940 Les Ulis, France		
RESPONSIBILITY	**NAME, TITLE & OFFICE**	**SIGNATURE**	**DATE**
Study Statistician	PPD Biotrial Biometrics 7-9 Rue Jean-Louis Bertrand 35042 Rennes Cedex, France		
IMPORTANT: This completed record (with additional sheets, where required), confirms the above-mentioned Statistical Analysis Plan version became the Final Statistical Analysis Plan			

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

TABLE OF CONTENTS

1 INFORMATION TAKEN FROM THE PROTOCOL 8
1.1 Study objectives 8
1.1.1 Primary objective 8
1.1.2 Secondary Objectives 8
1.1.3 Exploratory (ancillary study) Objective 8
1.2 Study design 8
1.2.1 Study population 8
1.2.2 Study duration 8
1.3 Methods and procedures 9
1.3.1 Subject identification and allocation to study treatment 9
1.3.2 Subjects assessments 9
1.3.2.1 Efficacy assessments 9
1.3.2.2 Biological evaluations 9
1.3.2.3 Safety assessments 9
1.3.2.4 Other Assessments 10
1.3.2.5 Withdrawal/discontinuation 11
1.3.3 Schedule of assessments 11
1.3.4 Planned sample size 14
2 SUBJECT POPULATIONS (ANALYSIS SETS) 14
2.1 Efficacy population 14
2.2 Screened population 14
2.3 Included population 14
2.4 Safety population 14
2.5 Intent-To-Treat (ITT) population 14
2.6 Per Protocol (PP) population 14
3 STATISTICAL METHODS 14
3.1 Statistical analysis strategy 14
3.1.1 Primary endpoint 15
3.1.2 Secondary endpoints 15
3.1.3 Safety endpoints 15
3.1.4 Exploratory endpoints 15
3.1.5 Multiplicity 15
3.1.6 Significance testing and estimation 15
3.2 Analysis methods 15
3.2.1 Efficacy 15
3.2.2 Biological and clinical evaluations 15
3.2.2.1 Biological evaluations 15
3.2.2.2 Clinical evaluations 16
3.2.3 Safety 17

3.2.3.1 Adverse events ... 17
3.2.3.2 Laboratory data ... 17
3.2.3.3 Physical examination ... 18
3.2.3.4 Vital signs ... 18
3.2.3.5 ECG ... 18
3.2.3.6 Pregnancy tests ... 19
3.2.4 Missing data and outliers ... 20
3.2.4.1 Missing data ... 20
3.2.4.2 Missing or incomplete dates ... 20
3.2.4.3 Outliers ... 20
3.2.5 Subject disposition ... 20
3.2.6 Withdrawals ... 21
3.2.7 Demographic and baseline characteristics ... 21
3.2.8 Medical and surgical history ... 21
3.2.9 Subject compliance ... 21
3.2.10 Prior and concomitant medications ... 22
3.2.11 Prior medications for Chronic Diarrhoea ... 22
3.2.12 Prior and concomitant non-drug therapies ... 22
3.2.13 Concomitant surgical procedures ... 22
3.2.14 Hospitalizations ... 22
3.2.15 Derived data ... 22
3.2.16 Rules and data formats ... 22
3.2.17 Pooling of Centres ... 23
3.2.18 Interim analysis ... 23
3.2.19 Role of data review committee (DRC) ... 23
3.2.20 Covariates and analysis of subgroups ... 23
4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS . 23
4.1 Hardware ... 23
4.2 Software ... 23
4.3 Validation programs ... 24
4.4 Restitution of the programs ... 24
5 CHANGES FROM PROTOCOL ... 24
6 REFERENCES ... 24
7 APPENDICES TO THE SAP TEMPLATE ... 25

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

HbA1c:	Haemoglobin A1c
AE:	Adverse Event
Ae:	Excreted Amount of Elemental Impurities cumulated in urine (ng)
ALP:	Alkaline Phosphatase
ALT:	Alanine aminotransferase
APTT:	Activated Partial Thromboplastin Time
AST:	Aspartate aminotransferase
ATC:	Anatomic Therapeutic Class
BLL:	Blood Lead Level
BMI:	Body Mass Index
CRF:	Case Report Form
CRU:	Clinical Research Unit
CV:	Coefficient of Variation
DBP:	Diastolic Blood Pressure
DRC:	Date Review Committee
eCRF:	Electronic Case Report Form
ECG:	Electrocardiogram
EI:	Elemental Impurities
EOS:	End Of Study
GGT:	Gamma-Glutamyl Transpeptidase
HBs Ag:	Hepatitis B surface antigen
HCV:	Hepatitis C antibody
HIV:	Human Immunodeficiency Virus
HR:	Heart Rate
ICH:	International Conference on Harmonisation
IMP:	Investigational Medicinal Product
INR:	International Normalised Ratio
ITT:	Intent-To-Treat
LLOQ:	Lower Limit Of Quantification
LOD:	Limit Of Detection
MCH:	Mean Cell Haemoglobin
MCHC:	Mean Cell Haemoglobin Concentration
MCV:	Mean Corpuscular Volume
MedDRA:	Medical Dictionary for Regulatory Activities

PP:	Per Protocol
PT:	Preferred Term
QRS:	QRS interval duration
QT:	Time interval for ventricular depolarisation and repolarisation
QTc:	Corrected QT interval
RBC:	Red Blood Cell
RR:	Respiratory Rate
SAP:	Statistical Analysis Plan
SAE:	Serious Adverse Event
SAS®:	Statistical Analysis System
SBP:	Systolic Blood Pressure
SD:	Standard Deviation
SI:	International System
SOC:	System Organ Class
TEAE:	Treatment Emergent Adverse Event
TID:	Three times a Day
TFLs:	Tables, Figures and Listings
ULOQ:	Upper Limit Of Quantification
VPCI:	Values of Potential Clinical Importance
WBC:	White Blood Cell
WHO-DD:	World Health Organisation – 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 assess the concentration of lead in blood, one of the Class I elemental impurities defined by International Conference on Harmonisation (ICH) Q3D guidelines, after chronic administration of Smecta® in subjects with chronic functional diarrhoea.

1.1.2 Secondary Objectives

The secondary objectives of the study are:

- To assess blood concentration of other Class I and IIa elemental impurities of interest (i.e. arsenic, cadmium, mercury, cobalt, vanadium, nickel and barium) and of aluminium after chronic administration of Smecta® in subjects with chronic functional diarrhoea.
- To assess urinary lead levels and urinary levels of other selected Class I and IIa elemental impurities of interest (i.e. arsenic, cadmium, mercury, cobalt, vanadium, nickel and barium), and aluminium after chronic administration of Smecta®.
- To further assess the safety and tolerance of Smecta® after chronic administration.

1.1.3 Exploratory (ancillary study) Objective

The ancillary study objective is to assess stools consistency and frequency during the screening period and after chronic administration of Smecta® in subjects with chronic functional diarrhoea.

The bowel microbiote composition will be assessed in a separate analysis plan.

1.2 Study design

This is a prospective, open-label, non-comparative, multi-centre, international phase I study, assessing the potential absorption of elemental impurities after chronic administration of Smecta® in subjects with chronic functional diarrhoea.

After a screening period of up to 6 weeks including a baseline assessment, each subject will be dosed with Smecta® three times a day (TID) over 5 weeks (Day 1 to Day 35) and then continue to be monitored over a post-treatment follow-up period of 3 months until end-of-study visit (EOS visit). Blood samples, urine collections and faces sampling will be obtained at screening phase and baseline visit, over the treatment period and then during follow-up period. Potential adverse events will be collected and monitored throughout the study.

1.2.1 Study population

A total of 35 subjects will be enrolled in order to ensure at least 29 subjects completing the study. It is planned to enrol a minimum of 40% of each gender, with gender distributed approximately equally between sites (e.g. no site with less than 35% of one gender).

1.2.2 Study duration

The overall study duration is expected to be approximately 8 months from first subject screened to last subject discharged from the study.

Each subject will be in the study for approximately 5 months, including 3 to 6 weeks for screening activities, 5 weeks of treatment, and 12 weeks of post-dose follow-up period.

1.3 Methods and procedures

1.3.1 Subject identification and allocation to study treatment

After informed consent is obtained, subjects who are screened will be allocated a subject number. All screened subjects must be identifiable throughout the study. The investigator will maintain a list of subject numbers and names in a source document to enable records to be found at a later date if required.

1.3.2 Subjects assessments

1.3.2.1 Efficacy assessments

There is no efficacy assessment in this study.

1.3.2.2 Biological evaluations

Blood Samples for Elemental Impurities and blood and plasma biobanking assessed at:

- Screening (Day -42 to Day -21),
- Day – 1 (Baseline),
- 6 samples at Day 1 and at Day 35:
  - 2 hours after the first dose,
  - immediately before second dose,
  - 3h post lunch dose,
  - immediately before the third dose,
  - 3h post evening dose,
  - 6h post evening dose,
- Day 2: On pre-dose before dosing,
- Days 8, 15, 22, and 29 visits: at pre-dose of any of the three dosing occasions of the day,
- Day 36, in the morning,
- Post-treatment follow-up period at Day 65, Day 95 and Day 125 (EOS visit)

Urine Collection (24-hour) for Elemental Impurities assessed at:

- Baseline (Day-1),
- Day 35,
- Post-treatment follow-up period at Day 65 and Day 95

Consistency of stools (Bristol scale) and frequency over 24h by subject assessed at:

- Screening (Day -42 to Day -21),
- Day -14,
- Baseline (Day-1),
- Day 8,
- Day 35,
- Post-treatment follow-up period at Day 65 and Day 95 and Day 125 (EOS visit)

1.3.2.3 Safety assessments

The safety assessments are:

- Adverse events (AEs) monitored from the time that the subject gives informed consent and throughout the study
- Clinical safety assessments:

- Physical examination at screening and EOS visit;
- Vital signs measured at screening and EOS visit, including supine systolic and diastolic blood pressure (SBP & DBP), heart rate (HR), body weight, and aural body temperature;
- 12-lead electrocardiograms (ECGs) measured at screening and EOS visit, including interpretation with clinical significance, sinus rhythm, respiratory rate (RR) interval duration or heart rate (HR), PR interval duration, QRS interval duration, time interval for ventricular depolarisation and repolarisation (QT) interval duration, corrected QT interval (QTc) interval corrected by the Bazett correction method;

- Clinical laboratory tests, including clinical significance, measured at screening, D-1 and EOS visit:
  - Haematology: full blood count including red blood cells (RBC) count, haemoglobin, haematocrit, mean corpuscular volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), white blood cell (WBC) count with differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), platelet count;
  - Blood biochemistry: urea, creatinine, total bilirubin, conjugated bilirubin, chloride, bicarbonate, sodium, potassium, calcium, inorganic phosphate, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), amylase, lipase, albumin, total protein, total cholesterol, triglycerides, fasting glucose, iron, transferrine saturation, ferritin, eGFR, haemoglobin A1c (HbA1c), urate, C reactive protein (only at screening);
  - Coagulation: activated partial thromboplastin time (APTT), prothrombin time, prothrombin ratio, international normalised ratio (INR);
  - Urinalysis: pH, proteins, ketones, glucose, bilirubin, urobilinogen, occult blood, Nitrite, Microscopic examination of sediment (if indicated)
  - Pregnancy tests at screening, D-1 and EOS visit

1.3.2.4 Other Assessments

- Demographics (country, sex, race, age) at screening;
- Body height, body weight and BMI at screening,
- Medical and surgical history at screening;
- Urine drug of abuse tests (cannabis and metabolites, cocaine, amphetamines, opiates, methamphetamines, barbiturates, benzodiazepines, methadone, ecstasy, and tricyclic antidepressants) at screening and Day-1;
- Alcohol breath test at screening and Day-1;
- Substance use (Alcohol, tobacco, caffeine and dietary habits) at screening;
- Serology: Hepatitis B surface antigen (HBs Ag), Hepatitis C antibody (HCV) and Anti-HIV1+2 antibodies at screening and Day-1;
- Post-menopausal status at screening;
- Prior and concomitant general medications, prior medications for chronic diarrhoea, prior and concomitant non-drug therapies and prior and concomitant surgical procedures;

1.3.2.5 Withdrawal/discontinuation

All subjects are free to interrupt or withdraw their consent to participate in the study at any time, for any reason, specified or non-specified, and without penalty.

A subject may also be discontinued from the study upon Sponsor's and/or Investigator's decision for any appropriate reason, such as safety related to an adverse event or concomitant therapy, major protocol deviation, noncompliance with protocol restrictions, etc. Due to the study primary objective it is important that subjects participating to the study comply with the full treatment and follow-up schedule. Hence their wish to take part to the study up to its end should be fully discussed and confirmed at study entry. This requirement is to ensure the study scientific value by ensuring the collection of the full set of data necessary for its analysis and does not preclude any subject right to withdraw at any time as stated above.

All cases of discontinuation will be discussed between the Investigator and the Sponsor or its representative.

1.3.3 Schedule of assessments

Here are the schedules of assessments extracted from the protocol:

Study Schedule of Events

	Screening	Treatment Period								Follow up Period		
Weeks:		1			2	3	4	5	5	9	13	17
Visits:	V1	V2			V3	V4	V5	V6	V7	V8	V9	V10 (EOS)
Days:	D-42 to D-21	D-1 (Baseline)	D1	D2	D8	D15	D22	D29	D35	D65	D95	D125
Time windows:		+/- 15 min			+/- 1d	+/- 1d	+/-1d	+/- 1d	+/- 1d	+/- 7d	+/- 7d	+/- 7d
Subjects' disposition:	Outpatient	Inpatient			out	out	out	out	inpat	inpat	inpat	out
Informed Consent, Demography, Medical & Surgical History, Prior Medications	X											
Safety Evaluations												
Physical exam (incl. Body Height/Weight [c]) and Vital Signs, aural body temperature	X											X
12-lead Electrocardiograms (ECGs)	X											X
Concomitant Medication & Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory (Haematology, Biochemistry, Coagulation and Urinalysis)	X[i]	X										X
Pregnancy Test (WOCBP only)[d]	X	X										X
Urine Drug Assay & Alcohol test	X	X										
Smecta® (TID, morning, noon, evening)			X[h]	----------	----------	----------	----------	----------	X[h]			
Biological Samples												
Blood Samples for Elemental Impurities and biobanking	X	X	X[a,e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[a,e]	X	X	X
Urine Collection (24-hour) for Elemental Impurities		X							X	X	X	
Faecal Samples for Microbiota	X[g]	X			X				X	X	X	X
Consistency of stools (Bristol scale) and frequency over 24h by subject[k]	X[j]	X			X[f]				X	X	X	X

a Six samples on Day 1 (and Day 35): 2 hours after the first dose (ex.: Smecta® intake 7.00am, meal 7.30am, PK 9.00am), immediately before second dose (ex.: PK 11.30am, Smecta® intake just after at 11h.30, meal at 12.30), 3h post lunch dose (ex.: PK at 2.30pm), immediately before the third dose (ex.: PK at 6.30pm, Smecta® intake just after at 6.30pm and meal 7.30pm), 3h post evening dose (ex.: PK at 9.30pm) and 6h post evening dose (ex.: 00.30am), and one sample on Day 36 in the morning (ex.: PK at 7.00am, Smecta® intake just after at 7.00am and meal 7.30am)

b On pre-dose before dosing (morning, approximately 7am on Day 2, and on pre-dose of any of the dosing occasion on the other days)

c Body height only at screening.

d Pregnancy test: serum at screening and urine at baseline and EoS.
e Time window for PK sampling: ± 15 min
f To be performed 24h before the visit 3
g 1 sample to be taken at screening visit at the CRU and 1 sample by the subject at home at Day-14 ±1 day
h Smecta® should be taken fasting and at least one hour before meal, except for breakfast at least 30 minutes before.
i C-reactive protein to be analysed only at screening
j Diary to be completed at screening retrospectively to cover the past 24h, and 24h before the Day-14 stool sample
k To the extent possible, to collect the data over approximately 24h preceding the stool sample taken at the visit 24h (i.e. 1 day or more).

1.3.4 Planned sample size

The critical limit of 50µg/l of lead is chosen as being the most conservative value taken among various guidelines (risk of saturnism, observations under high lead exposure at work). The baseline blood lead concentration of 31,4µg/l is considered as being a mean blood lead concentration in a survey of 1949 adults (18-74 years old) living in France in 2006-2007 (Falq et al. 2011). This population is representative of the French population including different socio-demographic characteristics and environment risk factors such as: sex, age, smoking status, type of drinking water, leisure activities, age of housing, shellfish/crustacean consumption. Considering the inclusion and exclusion criteria defined for the study, the enrolled subjects should have BLL levels in the same range as reported in the survey. With a standard error to the mean of [0,56], the mean blood lead concentration of 31.4µg/l is at confidence 95% to be found within [29.82; 32.98] under similar conditions. The non-superiority Δ margin is a clinical choice calculated as the difference of: 50 – 31.4 = 18.6µg/l. A precision of 15% (coefficient of variation) (CV) of the bioanalytical assay has been considered in the determination of sample size. Based on the above considerations, a sample size of 29 subjects with baseline mean blood lead concentration no greater than 36 µg/l (<36 µg/l), is required to provide 81% power to reject the null hypothesis of a difference of means no greater than 18,6 µg/l (≤ 18,6 µg/l considered as no difference of means). Considering potential drop-out, it is planned to enroll a total of 35 subjects to ensure that at least 29 subjects completed the study.

Subjects who prematurely discontinue after investigational medicinal product (IMP) administration will not be replaced.

2 SUBJECT POPULATIONS (ANALYSIS SETS)

2.1 Efficacy population

There is no efficacy assessment in this study.

2.2 Screened population

The screened population is all screened subjects in the study which have given an informed consent.

2.3 Included population

The included population is all included subjects in the study i.e. with a status “included” at the end of the baseline visit.

2.4 Safety population

The safety population is all subjects receiving at least one dose of study medication.

2.5 Intent-To-Treat (ITT) population

The ITT population is all subjects receiving at least one dose of study medication and having one pre-dose BLL and at least one post-dose BLL.

2.6 Per Protocol (PP) population

The Per Protocol population is all subjects in the ITT population who completed the last post-treatment follow-up visit without any major protocol deviation.

3 STATISTICAL METHODS

3.1 Statistical analysis strategy

The statistical analyses will be performed in accordance with ICH E9 guideline.

Statistical analyses described in this document will be performed by Biotrial Biometrics, Rennes, France.

3.1.1 Primary endpoint

The primary endpoint is to assess the absolute change in blood lead level (BLL) from baseline during treatment and post-treatment follow-up period.

3.1.2 Secondary endpoints

The secondary endpoints are to assess:

- the absolute change from baseline of concentrations of other selected Class I (i.e. arsenic, barium) and Class IIa elemental impurities (i.e.: cadmium, mercury, cobalt, vanadium, nickel) and aluminium in blood during treatment and post-treatment follow-up period.
- the absolute change from baseline of urinary concentrations of selected Class I and IIa elemental impurities (arsenic, barium, cadmium, mercury, cobalt, vanadium, nickel) and aluminium in urine at the end of Smecta® administration and during follow-up period.

3.1.3 Safety endpoints

The safety endpoints are:

- physical examination, vital signs, ECG,
- standard clinical laboratory tests,
- adverse events and treatment emergent adverse events (TEAE).

3.1.4 Exploratory endpoints

Different absolute changes from baseline will be described on the ITT population:

- Absolute changes from baseline of consistency of stools (as rated according to Bristol scale over 24h by the subject) and frequency at different study visits.
- The microbiota absolute changes analysis will be described in a specific and separate plan.

3.1.5 Multiplicity

There is no plan for multiple testing adjustments in this study.

3.1.6 Significance testing and estimation

The statistical analysis of safety and biological samples is only descriptive therefore no formal statistical significance testing will be performed.

3.2 Analysis methods

3.2.1 Efficacy

Not applicable.

3.2.2 Biological and clinical evaluations

3.2.2.1 Biological evaluations

Biological evaluations concern blood samples for elemental impurities, urine collection (24-hour) for elemental impurities.

The baseline for blood concentrations (lead and other elemental impurities) will be the average between the available screening and pre-dose (Day-1) values (as defined in Appendix 1 (5)).

For blood lead concentrations, absolute values and changes (as defined in Appendix 1 (6)) from BLL baseline will be summarized for all post-baseline time-points on the ITT and the PP population.

Additionally, for all follow-up time points, absolute changes from D36 (in the morning) will be calculated and summarized.

Corresponding listings will be provided on ITT population.

Plots of mean absolute changes over time (with 95% confidence interval) will be provided on ITT and PP population and individual corresponding plots on ITT population (one graph for full profile). For blood lead concentrations, same analyses by country will be presented.

For other elemental impurities blood concentrations, the analysis will also be described in the same way as for blood lead concentrations expect for plots of means and individual corresponding plots which will be provided only for arsenic and barium parameters.

The baseline for urine concentrations (lead and other elemental impurities) and Ae parameter will be defined as the last available (and reliable if applicable) assessment collected prior to receiving dose of Smecta® on Day 1.

For urine lead concentrations and other elemental impurities, the same approach for blood lead concentrations will be done expect that there will be no plots.

The cumulative amount of EI (Elemental Impurities) excreted in urine (the Ae parameter) will be calculated (as defined in Appendix 1 (7)) and summarized at each scheduled assessment with absolute changes from baseline and absolute changes from D36 (in the morning) and listed on ITT population. Plot of mean of this cumulative amount (with 95% confidence interval) will be provided on ITT population if the number of data above the limit of quantification is sufficient.

The volume of urine will be only listed on ITT population.

For summary statistics, the following will be presented: n, arithmetic mean with its 95% confidence interval, standard deviation (SD), median and the range (minimum, maximum).

Geometric mean with its 95% confidence interval, CV% and geometric CV% will also be presented.

To compute descriptive statistics, all <LOQ values are replaced by the numerical value (LOQ/2) throughout the dataset and all <LOD values are replaced by the numerical value (LOD/2) throughout the dataset.

In case of high blood level of lead at one or two of the baseline points, a sensitivity analysis may be performed for blood lead concentrations summary tables and figures, excluding the patients with such unexpected baseline results to avoid any confounding of the mean study results.

Modeling of lead levels in blood and urine may be performed if deemed necessary. If it is the case, the data analysis plan and the analysis will be reported in separate data analysis plan and report.

3.2.2.2 Clinical evaluations

Consistency of stools (Bristol scale) and frequency over 24h by subject will be assessed on ITT population.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to receiving dose of Smecta® on Day 1.

Number of watery stools (type 6 or 7), non-watery stools (type 1 to 5 inclusive) and total number of stools will be calculated for each subject and visit and will be summarised by visit with absolute changes from baseline.

Mean scores for watery stools, non-watery stools and for all stools will be calculated for each subject and visit and will be summarised by visit with absolute change from baseline. Corresponding individual listings will be provided.

Figures of means for numbers of stools and mean scores per visit on all subjects will be presented for watery stools, non-watery stools and total number of stools.

3.2.3 Safety

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

3.2.3.1 Adverse events

AEs reported in the case report form (CRF) will be coded using the medical dictionary for regulatory activities (MedDRA) Version 19.0 or higher.

All adverse events and SAEs, including pre-treatment events which occurred during the screening period will be reported from the time of consent until the EOS visit.

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

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

Treatment Emergent Adverse Events (TEAE) will be flagged (*) in the adverse events listing and will be summarised.

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

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

An overall summary table of all AEs will be presented.

TEAEs will be summarised with the number and percentage of subjects with adverse events classified by primary system organ class (SOC) and preferred term (PT). The number of occurrences of a TEAE will also be presented.

In addition, the same summary tables will also be presented for SAEs, TEAEs per decreasing frequency, TEAEs by maximum intensity, TEAEs by most serious causality and TEAEs leading to withdrawal.

In the event of multiple adverse events being reported by the same subject, the maximum intensity (severe > missing > moderate > mild) and the most serious causality (related > not related) will be chosen.

3.2.3.2 Laboratory data

A separate listing of normal ranges for international system (SI) units will be provided by gender and age where relevant.

Laboratory data (haematology, biochemistry, coagulation and urinalysis) will be listed in SI units and abnormal values will be flagged (High, [H], Low [L], clinically significant [CS]) where applicable. Any unscheduled laboratory assessments will be flagged [U] in the listings.

In addition, a listing will be presented of all values for a subject with at least one clinically significant abnormal laboratory value.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to receiving dose of Smecta® on Day 1.

For haematology, biochemistry and coagulation, summary statistics will be presented at each scheduled assessment and absolute changes from baseline. For haematology and biochemistry, shift tables from baseline to post baseline visit (EOS visit) will be presented using the number and percentage of subjects with low, normal or high values.

For continuous urinalysis, summary statistics will be presented at each scheduled assessment for actual values and absolute changes from baseline.

Categorical urinalysis parameters (absent/trace/positive) will be presented in frequency tables at each scheduled assessment as well as subjects with low, normal or high urinary values.

3.2.3.3 Physical examination

Physical examination will be listed by subject, timepoint and examination date.

3.2.3.4 Vital signs

Vital signs (supine systolic and diastolic blood pressure (SBP & DBP), heart rate (HR), body weight, and aural body temperature) will be listed at each assessment by subject (and so including clinically significant findings). Any unscheduled vital signs will be flagged [U] in the listing.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to receiving dose of Smecta® on Day 1.

Summary statistics will be presented at each scheduled assessment for actual values and absolute changes from baseline.

Shift tables for heart rate and blood pressure (systolic and diastolic) will be presented with the number and percentages of subjects with values of potential clinical importance (VPCI):

-Systolic blood pressure (mmHg) will have three categories:

<120	Low
[120-129]	Normal
>129	High

-Diastolic blood pressure (mmHg) will have three categories:

<80	Low
[80-84]	Normal
>84	High

-Heart rate (bpm) will have three categories:

<60	Low
[60-100]	Normal
>100	High

The VPCI will be flagged in the listings and the flagging identifier specified.

The temperature will be listed by subject, timepoint and examination date.

3.2.3.5 ECG

Interpretation with clinical significance, sinus rhythm, respiratory rate (RR) interval duration or heart rate (HR), PR interval duration, QRS interval duration, time interval for ventricular depolarisation and repolarisation (QT) interval duration, corrected QT interval (QTc) corrected by the Bazett correction method will be presented.

ECG results will be listed at each assessment by subject (and so including clinically significant findings).

Any unscheduled ECGs will be flagged [U] in the listing.

The baseline will be defined as the last available (and reliable if applicable) assessment collected prior to receiving dose of Smecta® on Day 1.

For continuous ECG parameters (RR, PR, QRS, QT and QTcB), summary statistics will be presented at each scheduled assessment for actual values and absolute changes from baseline.

Shift tables for heart rate, PR interval duration, QRS interval duration, QT interval duration and corrected QT interval will be presented with the number and percentages of subjects with values of potential clinical importance (VPCI):

-Heart rate (bpm) will have three categories:

<60	Low
[60-100]	Normal
>100	High

- PR interval duration (s) will have three categories:

<0.12	Low
[0.12-0.20]	Normal
>0.20	High

- QRS interval duration (s) will have two categories:

≤0.12	Normal
>0.12	High

- QT interval duration (s) will have two categories by each gender stratum:

Gender stratum	Normal	High
Males	<0.40	≥0.40
Females	<0.44	≥0.44

- Corrected QT interval (ms) will have two categories by each gender stratum:

Gender stratum	Normal	High
Males	≤440	>440
Females	≤460	>460

The VPCI will be flagged in the listings and the flagging identifier specified.

For interpretation of clinical significance (within normal limits / abnormal, not clinically significant / abnormal, clinically significant / not evaluable), a frequency table will be presented, by visit.

3.2.3.6 Pregnancy tests

A listing with the date of examination, the status of the examination (done/not done/not applicable) and the result (positive/negative) will be provided by subject, timepoint, examination date and method: (serum on screening only or urine).

3.2.4 Missing data and outliers

3.2.4.1 Missing data

No missing value will be imputed.

If a value required a retest, the last reliable non-missing value will be taken into account if measured before the administration of Smecta®; and the first non-missing reliable value for post-baseline assessments. An assessment will be considered reliable if it is performed without any technical problem and if the result is within the range of plausible values.

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

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

3.2.4.2 Missing or incomplete dates

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

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

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

If a partial date and the associated information do not allow to state about the assignation to a group / category, all the possible groups / categories will be considered (e.g. a medication with partial start and stop dates could be considered as prior and concomitant treatment).

Where this is possible, the derivations based on a partial date will be presented as superior inequalities (e.g. for an AE started in 2004-02 after the administration performed on 2004-01-31, 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).

3.2.4.3 Outliers

Any outlier which is implausible 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.

3.2.5 Subject disposition

A summary table with the description of the number of subjects in each analysis set (Screened Set, Included Set, Safety Set, ITT set and PP set) will be performed by country and overall.

A summary table with the description of the numbers of screened subjects, screening failure subjects, included subjects, treated subjects, study completed subjects (who completed the last post-treatment follow-up visit) and the number of subjects who discontinued classified by main reason of withdrawal will be performed. A figure for subject disposition and corresponding individual listings will be provided.

A summary table with the number and percentage of subjects at each visit will be performed on the safety set.

Listing with dates of assessments will also be carried out on the included population.

A listing of the inclusion and exclusion criteria not met will be provided by subject, and subject eligibility will also be listed on the included population.

A summary table will present the extent of subject duration in the study (in weeks) for all the subjects in the safety population (as defined in Appendix 1 (2)).

A listing of their study duration (in weeks) will be presented by subject on the safety population.

Listing of re-enrollment of subjects will be listed separately on included population.

3.2.6 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.

3.2.7 Demographic and baseline characteristics

All demographic (country, sex, race) and baseline characteristics (age, body height, body weight and BMI at baseline) as well as the substance use (alcohol, tobacco, caffeine and dietary habits use) will be listed by subject on the safety population.

Summary statistics will be provided for demographic and baseline characteristics as well as the substance use on the safety population.

For demographic and baseline characteristics, the results will be described by gender and by country.

The results of urine drug of abuse tests, alcohol breath test, post-menopausal status (at screening), and serology (at screening and Day-1) will only be provided in subjects data listings on the safety population by subject and examination date.

3.2.8 Medical and surgical history

Medical and surgical history will be coded using MedDRA Version 19.0 or higher.

Listings will present the primary system organ class, the preferred term and the reported term. The listings will be sorted by subject, start date, primary system organ class, preferred term and reported term on the safety population.

A frequency table of the number and percentage of subjects will be provided for all medical and surgical history by primary system organ class and preferred term for the safety population.

3.2.9 Subject compliance

The time and day of drug administration will be recorded by the study site when present at the clinical unit and by the subject when self-administered using a diary.

Compliance to diosmectite (Smecta®) intake will be based on this diary.

All treatment administration information will be listed by subject, timepoint and date of administration on the safety population.

Three listings will be performed: one for the treatments taken, one for the meals taken, and one for the drug accountability.

Study drug exposure (as defined in Appendix 1 (3)) in weeks will be summarized.

A summary table will present the global compliance (expressed in percentage as defined in Appendix 1 (4)) on the treatment period for the safety population.

Additionally, compliance will be categorized as follows: < 80% (Under compliance), 80-120% (Compliance) and > 120% (Over compliance) and will be summarized.

In the included population, protocol deviations from observed and scheduled times will be presented with the reasons for exclusion from the PP population.

All the protocol deviations identified will be also listed by subject with the reasons for exclusion.

A protocol deviation specification document will be provided further by Aepodia.

3.2.10 Prior and concomitant medications

Concomitant medication will be coded by using the World Health Organisation – Drug Dictionary (WHO-DD) June 2016 Version or higher.

The therapeutic class will correspond to the second level of anatomic therapeutic class (ATC) code, that is, corresponding to the first 3 figures.

The date and time of baseline (Smecta® on Day 1) will be used as the cut-off date for the definition of prior and concomitant medications:

A prior medication will be defined as a medication stopped prior to the date of baseline.

A concomitant medication will be defined as a medication which is taken by subject any time during the study after the date of baseline.

A medication that started before the date of baseline and is continuing after will be considered as both, prior and concomitant.

Prior, concomitant and both prior and concomitant medications will be flagged P, C and PC respectively, in all listings.

Listings will be presented for the therapeutic class, preferred name and reported name on the safety population. The listings will be sorted by subject, chronological start date, therapeutic class, preferred name and reported name.

Frequency tables of the number and percentage of subjects with at least one prior or, concomitant medication will be provided by therapeutic class and preferred name on the safety population.

3.2.11 Prior medications for Chronic Diarrhoea

Analysis of prior medications for chronic diarrhoea will be performed as described in section 3.2.10.

3.2.12 Prior and concomitant non-drug therapies

Prior and concomitant non-drug therapies will be coded using MedDRA Version 19.0 or higher. It will be listed by subject, chronological start date, primary system organ class, preferred term, and reported term.

3.2.13 Concomitant surgical procedures

Concomitant surgical procedures will be coded using MedDRA Version 19.0 or higher. It will be listed by subject, chronological start date, primary system organ class, preferred term, and reported term.

3.2.14 Hospitalizations

Dates of hospitalizations occurring during the study will be listed on included population with reported term, entry date, and discharge date.

3.2.15 Derived data

The derived data are variables which are calculated from the raw data in the electronic case report form (eCRF) and not included in the database and will be included in the listings.

3.2.16 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 with the number of decimal places collected, and derived data will be presented to an appropriate

number of decimal places. The appropriate number of decimal places will be determined by general practice, mathematical rationale or scientific rationale (e.g. age should be presented in whole numbers).

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

Mean, median and standard deviation values will be reported with 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.

CV% and ratio will be presented with one decimal place.

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

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].

3.2.17 Pooling of Centres

Two countries (one centre for each) are planned to be involved: Netherlands and United Kingdom.

3.2.18 Interim analysis

No formal preliminary or interim analyses are planned for this study. If an unplanned preliminary or interim analysis is deemed necessary, the Sponsor clinical pharmacologist or Investigator will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

Blood lead concentrations from screening and baseline (Day-1) will be obtained on an ongoing basis to verify that these values are within the 95% confidence interval of the mean blood lead concentration of 31,4µg/l used in the determination of sample size (see Section 8.1.2) and therefore confirm the assumptions for sample size calculation. If not, the sample size might be re-evaluated accordingly.

3.2.19 Role of data review committee (DRC)

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

3.2.20 Covariates and analysis of subgroups

No covariates or analysis of subgroups are planned in this study.

Nevertheless, analyses by country (Netherlands and United Kingdom) will be presented for demographic and baseline characteristics and also for blood lead concentrations.

4 COMPUTER SYSTEMS, SOFTWARE AND VALIDATION OF PROGRAMS

4.1 Hardware

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

4.2 Software

All tables, figures and listings (TFLs) will be produced and statistical analysis performed using statistical analysis system (SAS®)) version 9.4 [2]. All outputs will be provided as individual word 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 Biometrics will provide a validation plan to Ipsen identifying the methods of validation.

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

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

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

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

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

4.4 Restitution of the programs

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

5 CHANGES FROM PROTOCOL

Changes from the final protocol dated 7 September 2016 are the following:

Results of plasma samples will not be analysed during the study therefore will not be included in the clinical study report neither the biobanking blood samples of other elemental impurities that may be dosed after the study upon need or request from Health Agencies.

Since there was no eligibility criterion on blood lead level at study entry, some dosages could evidence an unexpected elevated level at baseline.

In the protocol, hypothesis for sample size calculation was based on the mean value in literature data in France (Falq et al. 2011).

In case of high blood level of lead at one or two of the baseline points, a sensitivity analysis may be performed.

This analysis will exclude the patients with such unexpected baseline results to avoid any confounding of the mean study results.

6 REFERENCES

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

2. SAS, Version 9.4. SAS Institute Inc., Cary, NC, USA, 2012.

7 APPENDICES TO THE SAP TEMPLATE

Appendix 1: Derived Data

The following derived data will be calculated:

(1) Study day

Study day will be defined as '-1' for the day prior to IMP administration and as '1' for the day of IMP administration (i.e. day 0 does not exist).

(2) Study duration

Study duration (weeks) will be calculated as [(last visit attended - date of first IMP administration) + 1] / 7.

(3) Study drug exposure

Study drug exposure (weeks) will be derived using information from diary and will be calculated as [(last date of IMP administration - first date of IMP administration) + 1] / 7.

(4) Compliance

Compliance (%) will be calculated as (the total number of sachets taken / the total number of expected sachets to be taken) x 100.

The total number of sachets taken will be derived using information from diary as the sum of number of sachets taken when a date of IMP administration is entered.

The total number of expected sachets to be taken will be derived using information from diary based on three sachets per day (TID) (morning, noon, and evening) to be taken by the subject as [(last date of IMP administration - first date of IMP administration) + 1] x 3.

(5) Baseline

BLL baseline will be derived as the average between the available screening and pre-dose (Day-1) values.

Baseline for other parameters will be derived as the last available (and reliable if applicable) assessment before IMP administration.

(6) Absolute change from baseline

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

(7) Ae parameter

Ae parameter (ng) will be calculated as the cumulated concentration of EI in urine × the total volume of urine collected over 24 hours.

(8) Therapeutic Class

The therapeutic class will correspond to the first 3 digits of the ATC code. The decoding of the therapeutic class will be done from the WHO-DD June 2016 Version or higher.

(9) Prior and concomitant medication duration

If the start and end dates of the medication are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration of concomitant treatments will be calculated as (end date/time - start date/time). If at least one time is missing, the duration of concomitant treatments will be calculated as (end date - start date) + 1. If the recorded end date is continuing at the end of the study then the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date –

start date) + 1" day(s). If the start date or the end date are partial, the duration will be presented as an inequality "≥xx" day(s) [i.e. ≥2 where start date=2004-01-31 and end date=2004-02 or start date=2004-01 and end date=2004-02-01] but if both are partial or one is missing the duration will not be presented.

(10) AE duration

If the start and end dates of the AE are identical then "<1" day will be presented with the duration in hh:mm recorded in the eCRF if it is available. If times are available, the duration will be calculated as (end date/time – start date/time) and presented in days hh:mm. If at least one time is missing and if the duration is greater than 24 hours then it will be calculated as (end date - start date) + 1 and presented in days. If the recorded end date is continuing at the end of the study, the end date will be listed as "ongoing" and the duration will be approximated as "≥(last attended visit date – start date) + 1" day(s). If the start date or the end date are partial the duration will be presented as a superior inequality "≥xx" day(s) [i.e. ≥2 where start date=2004-01-31 and end date=2004-02 or start date=2004-01 and end date=2004-02-01].

(11) Time since last dose for adverse event

If the start date of the adverse event is identical to the date of last administration, then"<1" day will be presented with the time to onset in hh:mm recorded in the eCRF if it is available. If times are available, the time will be calculated as (start date/time – last administration date/time) and presented in days hh:mm. If at least one time is missing and if the time to onset is greater than 24 hours then it will be calculated as (start date - last administration date)+1 and presented in days. If the start date and the associated information do not allow to state about the last dose received (partial start date or start at administration day without knowing if it started before or after the drug intake), all the possible time since last dose will be presented [i.e.: if a subject received a daily administration and reported an AE at second administration day but without indication about before or after the drug intake the time since last dose will be as "2 / <1"]. If the start date is partial, the time since last dose will be presented as an superior inequality (i.e.: for an AE started in 2004-02 after the only administration performed on 2004-01-31, the time since last dose will be as "≥2" days). If the start date is missing the time since last dose will not be presented although the AE will be assigned to each dose received before its end date.

Appendix 2: List of TFLs

Listings index

16.1.7 Randomisation Scheme and Codes

Not applicable

16.2 SUBJECT DATA LISTINGS

16.2.1 Discontinued subjects

Listing 16.2.1.1: Subject Disposition – Screened Population

Listing 16.2.1.2: Subject Disposition – Study Withdrawals – Screened Population

Listing 16.2.1.3.1: Inclusion Criteria Assessments

Listing 16.2.1.3.2: Inclusion Criteria not Met – Included Population

Listing 16.2.1.4.1: Exclusion Criteria Assessments

Listing 16.2.1.4.2: Exclusion Criteria not Met – Included Population

Listing 16.2.1.5: Assessments Dates – Included Population

Listing 16.2.1.6: Re-enrollment of Subjects – Included Population

16.2.2 Protocol deviations

Listing 16.2.2.1: Subject Eligibility for the Study – Included Population

Listing 16.2.2.2: Major and Minor Protocol Deviations – Included Population

Listing 16.2.2.3: Reasons for Exclusion from the Populations – Included Population

16.2.3 Subjects excluded from the efficacy analysis

Not applicable

16.2.4 Demographic data

Listing 16.2.4.1: Demographics and Baseline Characteristics – Safety Population

Listing 16.2.4.2: Alcohol Breath Test – Safety Population

Listing 16.2.4.3: Urine Drug of Abuse Tests – Safety Population

Listing 16.2.4.4: Substance Use – Safety Population

Listing 16.2.4.5: Serology – Safety Population

Listing 16.2.4.6: Postmenopausal Status – Safety Population

Listing 16.2.4.7.1: Medical and Surgical History – Reported Terms and Associated MedDRA Terms – Safety Population

Listing 16.2.4.7.2: Medical and Surgical History – Safety Population

Listing 16.2.4.8.1: Prior and Concomitant Medications – WHO-DD Names – Safety Population

Listing 16.2.4.8.2: Prior and Concomitant Medications – Safety Population

Listing 16.2.4.9.1: Prior Medications for Chronic Diarrhoea – WHO-DD Names – Safety Population

Listing 16.2.4.9.2: Prior Medications for Chronic Diarrhoea – Safety Population

Listing 16.2.4.10.1: Prior and Concomitant Non-Drug Therapies – Reported Terms and Associated MedDRA Terms – Safety Population

Listing 16.2.4.10.2: Prior and Concomitant Non-Drug Therapies – Safety Population
Listing 16.2.4.11.1: Concomitant Surgical Procedures – Reported Terms and Associated MedDRA Terms – Safety Population
Listing 16.2.4.11.2: Concomitant Surgical Procedures – Safety Population

16.2.5 Compliance

Listing 16.2.5.1: Study Treatment Administration – Safety Population
Listing 16.2.5.2: Meals – Safety Population
Listing 16.2.5.3: Drug Accountability – Safety Population
Listing 16.2.5.4: Study Drug Compliance – Safety Population
Listing 16.2.5.5: Study Duration – Safety Population

16.2.6 Biological and Clinical Evaluations Data

Listing 16.2.6.1.1: Individual Blood Concentrations of Lead (Raw Data) – ITT Population
Figure 16.2.6.1.2: Individual Graphs for Blood Concentrations of Lead – ITT Population
Listing 16.2.6.2: Individual Blood Concentrations of Other Selected Class I Elemental Impurities and Class IIa Elemental Impurities and Aluminium in Blood (Raw Data) – ITT Population
Figure 16.2.6.3: Individual Graphs for Blood Concentrations of Arsenic and Barium – ITT Population
Listing 16.2.6.4: Individual Urine Concentrations of Lead (Raw Data), Cumulative Amount of Elemental Impurities Excreted and Volume of Urine – ITT Population
Listing 16.2.6.5: Individual Urine Concentrations of Other Selected Class I Elemental Impurities and Class IIa Elemental Impurities and Aluminium in Urine (Raw Data) – ITT Population
Listing 16.2.6.6: Consistency of Stools and Frequency – ITT Population
Listing 16.2.6.7: Number and Mean Scores for Stools – ITT Population

16.2.6 Efficacy data

Not applicable

16.2.7 Adverse event listings

Listing 16.2.7.1: Adverse Events Key Information
Listing 16.2.7.2: All Adverse Events – Safety Population
Listing 16.2.7.3: Serious Adverse Events – Safety Population
Listing 16.2.7.4: Adverse Events Leading to Withdrawal – Safety Population

16.2.8 Listing of individual laboratory measurements by subject

Listing 16.2.8.1: Normal Ranges for SI Units
Listing 16.2.8.2: Haematology (SI Units) (Raw Data) – Safety Population
Listing 16.2.8.3: Biochemistry (SI Units) (Raw Data) – Safety Population
Listing 16.2.8.4: Coagulation (SI Units) (Raw Data) – Safety Population
Listing 16.2.8.5: Urinalysis (SI Units) (Raw Data) – Safety Population

Listing 16.2.8.6: Pregnancy Test – Safety Population

16.2.9 Listing of other safety data

Listing 16.2.9.1: Assessment of Physical Examination – Safety Population

Listing 16.2.9.2: Vital Signs (Raw Data) – Safety Population

Listing 16.2.9.3: 12-lead ECG (Raw Data) – Safety Population

16.2.10 Listing of hospitalization Dates – Included Population

Tables index

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

Table 14.1.1: Subjects Populations – Screened Population
Table 14.1.2.1: Subjects Disposition – Screened Population
Figure 14.1.2.2: Subjects Disposition – Screened Population
Table 14.1.3: Reasons for Screening Failure – Screened Population
Table 14.1.4.1: Major and Minor Protocol Deviations – Included Population
Table 14.1.4.2: Reasons for Exclusion from the Populations – Included Population
Table 14.1.5: Subjects Disposition by Visit – Safety Population
Table 14.1.6: Study Duration – Safety Population
Table 14.1.7.1: Demographics and Baseline Characteristics (Overall and by Gender) – Safety Population
Table 14.1.7.2: Demographics and Baseline Characteristics (by Country) – Safety Population
Table 14.1.8: Substance Use – Safety Population
Table 14.1.9: Medical and Surgical History – Safety Population
Table 14.1.10: Prior and Concomitant Medications – Safety Population
Table 14.1.11: Prior Medications for Chronic Diarrhoea – Safety Population
Table 14.1.12: Study Drug Exposure and Compliance – Safety Population

14.2 BIOLOGICAL AND CLINICAL EVALUATIONS DATA

14.2.1 Biological Evaluation – ITT population

Table 14.2.1.1.1*1*: Blood Concentrations of Lead (Summary Statistics) – ITT Population
Table 14.2.1.1.1.2: Sensitivity Analysis - Blood Concentrations of Lead (Summary Statistics)
Figure 14.2.1.1.2*.1*: Graph for Arithmetic Means of Blood Concentrations of Lead (with 95% Confidence Interval) – ITT Population
Figure 14.2.1.1.2.2: Sensitivity Analysis - Graph for Arithmetic Means of Blood Concentrations of Lead (with 95% Confidence Interval)
Table 14.2.1.2.1: Blood Concentrations of Other Selected Class I Elemental Impurities and Class IIa Elemental Impurities and Aluminium in Blood (Summary Statistics) – ITT Population
Figure 14.2.1.2.2: Graph for Arithmetic Means of Blood Concentrations of Arsenic and Barium (with 95% Confidence Interval) – ITT Population
Table 14.2.1.3: Urine Concentrations of Lead (Summary Statistics) – ITT Population
Table 14.2.1.4: Urine Concentrations of Other Selected Class I Elemental Impurities and Class IIa Elemental Impurities and Aluminium in Urine (Summary Statistics) – ITT Population

Table 14.2.1.5: Cumulative Amount of Elemental Impurities Excreted in Urine (Summary Statistics) – ITT Population

Table 14.2.1.6: Graph for Arithmetic Means of Cumulative Amount of Elemental Impurities Excreted in Urine (with 95% Confidence Interval) – ITT Population

14.2.2 Biological Evaluation – PP population

Table 14.2.2.1.1.*1*: Blood Concentrations of Lead (Summary Statistics) – PP Population

Table 14.2.2.1.1.2: Sensitivity Analysis - Blood Concentrations of Lead (Summary Statistics)

Figure 14.2.2.1.2.*1*: Graph for Arithmetic Means of Blood Concentrations of Lead (with 95% Confidence Interval) – PP Population

Figure 14.2.2.1.2.2: Sensitivity Analysis - Graph for Arithmetic Means of Blood Concentrations of Lead (with 95% Confidence Interval)

Table 14.2.2.2.1: Blood Concentrations of Other Selected Class I Elemental Impurities and Class IIa Elemental Impurities and Aluminium in Blood (Summary Statistics) – PP Population

Figure 14.2.2.2.2: Graph for Arithmetic Means of Blood Concentrations of Arsenic and Barium (with 95% Confidence Interval) – PP Population

Table 14.2.2.3: Urine Concentrations of Lead (Summary Statistics) – PP Population

Table 14.2.2.4: Urine Concentrations of Other Selected Class I Elemental Impurities and Class IIa Elemental Impurities and Aluminium in Urine (Summary Statistics) – PP Population

14.2.3 Clinical Evaluation study

Table 14.2.3.1: Consistency of Stools and Frequency Over 24 Hours – ITT Population

Figure 14.2.3.2: Graph of Means (±SEM) for Numbers of Stools – ITT Population

Figure 14.2.3.3: Graph of Means (±SEM) for Mean Scores of Stools – ITT Population

14.3 SAFETY DATA

14.3.1 Displays of adverse events

Table 14.3.1.1: Overall Summary of Adverse Events – Safety Population

Table 14.3.1.2: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term – Safety Population

Table 14.3.1.3: Number (%) of Subjects Reporting Serious Adverse Events by Primary System Organ Class and Preferred Term – Safety Population

Table 14.3.1.4: Number (%) of Subjects Reporting Treatment Emergent Adverse Events Leading to Withdrawal by Primary System Organ Class and Preferred Term – Safety Population

Table 14.3.1.5: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Decreasing Frequency of Preferred Term – Safety Population
Table 14.3.1.6: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Maximum Intensity – Safety Population
Table 14.3.1.7: Number (%) of Subjects Reporting Treatment Emergent Adverse Events by Most Serious Causality – Safety Population

14.3.2 Listings of deaths, other serious and significant adverse events

14.3.3 Narratives of deaths, other serious and certain other significant adverse events

14.3.4 Abnormal laboratory value listing

Listing 14.3.4.1: Haematology (SI Units): Abnormal Clinically Significant Values – Safety Population
Listing 14.3.4.2: Biochemistry (SI Units): Abnormal Clinically Significant Values – Safety Population
Listing 14.3.4.3: Coagulation (SI Units): Abnormal Clinically Significant Values – Safety Population
Listing 14.3.4.4: Urinalysis (SI Units): Abnormal Clinically Significant Values – Safety Population

14.3.5 Laboratory measurements

Table 14.3.5.1.1: Haematology (Summary Statistics) – Safety Population
Table 14.3.5.1.2: Haematology (Shift Tables) – Safety Population
Table 14.3.5.2.1: Biochemistry (Summary Statistics) – Safety Population
Table 14.3.5.2.2: Biochemistry (Shift Tables) – Safety Population
Table 14.3.5.3: Coagulation (Summary Statistics) – Safety Population
Table 14.3.5.4.1: Urinalysis – Quantitative Parameters (Summary Statistics) – Safety Population
Table 14.3.5.4.2: Urinalysis – Parameters (Frequency Tables) – Safety Population

14.3.6 Other safety data

Table 14.3.6.1.1: Vital Signs (Summary Statistics) – Safety Population
Table 14.3.6.1.2: Vital Signs (Shift Tables) – Safety Population
Table 14.3.6.2.1: ECG (Summary Statistics) – Safety Population
Table 14.3.6.2.2: ECG (Shift Tables) – Safety Population
Table 14.3.6.2.3: ECG (Interpretation of Clinical Significance) – Safety Population