Protocol Title:

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

Protocol D-FR-00250-108

Protocol Amendment #2 Version 4.0, dated 07-SEPT-2016

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EUDRACT number: 2016-002111-18

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Study Conduct Compliance Statement

This study will be conducted in compliance with the protocol, in accordance with the International Conference on Harmonisation Good Clinical Practice (CPMP/ICH 135/35) together with such other good clinical practice requirements and the ethical principles that have their origin in the Declaration of Helsinki, as well as with all currently applicable laws and regulations of the country where the study will be conducted.

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Agreement on Protocol – Signature Page

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

Protocol Version Number: 4.0

Protocol Version Date: **07-SEPT-2016**

By signing below, I hereby confirm that I have read, discussed and understood the above mentioned version of the protocol **D-FR-00250-108** and the background information concerning the study drug. I attest that I will carry out the study according to this protocol.

I also agree that the work will be performed according to Good Clinical Practice (GCP) guidelines, the ethical principles, and all currently applicable laws and regulations of the country(ies) where the study will be conducted.

Investigator

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SYNOPSIS

Title	ASSESSMENT OF ELEMENTAL IMPURITIES LEVEL AFTER CHRONIC ADMINISTRATION OF DIOSMECTITE (SMECTA®) IN SUBJECTS WITH CHRONIC DIARRHOEA
Study Alias	**D-FR-00250-108**
EudraCT Number	**2016-002111-18**
Investigational Product	Diosmectite (Smecta®)
Type of Study	Phase I, open label, non comparative study to assess the level of the Class I and IIa elemental impurities as defined by ICHQ3D* (e.g. lead, arsenic, cadmium…) in blood and urine samples after chronic administration of Smecta® in subjects with chronic diarrhoea. *ICHQ3D is a new guidance developed to provide a global policy for limiting elemental impurities in drug products and ingredients. As lead is a naturally constituent of Smecta®, present in a significant amount, and a Class I elemental impurities, the level of this element has been selected as the primary endpoint.
Investigational Site	The study will be performed in multiple Clinical Research Units in Europe.
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 5,5 months, including 3 to 6 weeks for screening activities, 5 weeks of treatment, and 12 weeks of post-dose follow-up period.
Objectives	Primary: • To assess the concentration of lead in blood, one of the Class I elemental impurities defined by ICH Q3D guidelines, after chronic administration of Smecta® in subjects with chronic functional diarrhoea. Secondary: • 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. Exploratory (ancillary study): • To assess the bowel microbiote composition, stools consistency and frequency after chronic administration of Smecta® in subjects with chronic functional diarrhoea. • Additional blood samples will be biobanked in order to further potentially assay other elemental impurities levels (see Attachment #5); • Plasma samples will be biobanked in order to further potentially assay lead in plasma.
Endpoints	Primary Endpoints: • Changes in BLL from baseline during treatment and post-treatment follow-up period. Secondary Endpoints: • Change from baseline of concentrations of other selected Class I elemental

	impurities (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. • 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. • Safety Endpoints: o physical examination, vital signs, ECG, o standard clinical laboratory tests, o adverse events and Treatment Emergent Adverse Events (TEAE) o additional medical monitoring visit at the discretion of the Investigator and in case of adverse reactions. <u>Exploratory endpoints:</u> • Change from baseline of the microbiote characteristics during Smecta® treatment and follow up. • Change from baseline of consistency of stools (as rated according to Bristol scale over 24h by the subject) and frequency at different study visits. • Change from baseline of blood and urine dosages of other elemental impurities as lithium (Li), antimony (Sb), molybdenium (Mo), copper (Cu), Tin (Sn) and chromium (Cr) at the end of Smecta® administration and during follow-up period. • Change from baseline of plasma concentration of lead at the end of Smecta® administration and during follow-up period
Study Design	Prospective, open label, non-comparative study with treatment of Diosmectite (Smecta®, 3g) TID over 5 weeks.
Number of Subjects	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).
Treatment: route, strength, regimen	Diosmectite (Smecta® 3g/sachet, powder for oral suspension. Three sachets per day (TID), morning, noon, and evening. For the purpose of this study, Smecta® should be taken fasting and at least one hour before meal, except for breakfast at least ½ hour before.
Reference/Control Treatment: route, strength, regimen	NA
Drug administration	Smecta® orange/vanilla 3g, sachet to be put in suspension in a glass of water.
Main Inclusion/Exclusion Criteria	- Male or female subjects, between 18 and 60 years old inclusive, BMI between 19 and 32 kg/m^2 inclusive (minimum body weight of 50 kg at screening). - Functional chronic diarrhoea defined as loose or watery stools occurring in at least 75% of stools for the last 3 months (with symptom onset at least 6 months before diagnosis). - No history of suspected organic or drug induced cause to chronic diarrhoea.
Study Evaluation Criteria: Impurities concentrations in blood and in urine and Safety	<u>Blood lead levels (BLL)</u> timepoints: • Screening (Day -42 to Day -21) • Day – 1 (Baseline) • Day 1 and 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 (morning, approximately 8am) • 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: - Day 65, Day 95, and Day 125 (end-of-study) <u>Urine collections (24-hour) at:</u> • Baseline (Day-1), • Day 35, • Post-treatment follow-up period: Day 65 and Day 95 <u>Safety Endpoints</u> will be assessed at different timepoints: • physical examination, vital signs, ECG, • clinical laboratory blood tests, • Adverse Events and Treatment Emergent Adverse Events (TEAE).
Lead and other elemental impurities levels reporting Methodology	Blood lead and urine lead levels will be measured by a validated bioanalytical assay inductively coupled plasma mass spectrometry (ICP-MS). Blood Lead Level (BLL) and other elemental impurities levels will be reported as well as uLL (urinary lead level) and plasma lead levels.
Statistical Methodology: elemental impurities, population definitions, and Safety	All available data will be descriptively analysed as one treatment cohort. BLL (and other elemental impurities) at the Screening and pre-dose (Day-1) will be averaged and considered as the BLL Baseline. BLL and change from baseline at each time points will be reported. Descriptive statistics will be reported for those parameters. uLL (urinary lead level) at baseline and at each time point will be reported. Change from baseline of uLL at each time point will be reported. Descriptive statistics will be reported for those parameters Safety population: Any subject receiving at least one sachet of Diosmectite will be analysed for safety Intent-to-treat (ITT) population: All subject receiving at least one sachet of Diosmectite and having one pre-dose BLL and at least one post-dose BLL Per protocol population: All subjects who completed the last post-treatment follow-up visit. Interim analyses: no formal interim analyses are planned to be conducted during the study. However BLL at screening and pre-dose, as well BLL obtained during the study will be analysed and reviewed on an ongoing basis for potential study adjustments (e.g.: check the assumptions taken for sample size calculation).

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RATIONALE FOR PROTOCOL AMENDMENT #2

The overall changes and rationale for the changes made to this protocol are as follows:

- To add 4 timepoints assessments for the consistency of stools (according to Bristol scale) and frequency over 24 hours as assessed by the subject at screening, Day-14, Day 65 and Day 125.
- To clarify the sampling methodologies for the assessment of elemental impurities.
- To modify a mistake in the Attachment 3 regarding the number of blood samples for the assessment of elemental impurities in blood: 23 samples to be taken (instead of 22 samples), leading to a small increase in the total maximum volume of blood to be collected during the study (from 322 ml to 330 ml).
- Modifications of the Global Patient Safety contact details

All modifications are presented in the Attachment 8.

PROTOCOL HISTORY

Protocol version	Rationale for amendment
V.2.0, 11JUL2016	NA – initial version
V.3.0, 08AUG2016, Amendment #1	• Clarification on the conditions for Study site discontinuation and Study Termination requested by the Ethics Committee in Netherlands in order to be more in line with the contract signed between Aepodia and the local Clinical Research Unit. • To modify a typo in the Exclusion criterion # 23 regarding the Hepatitis C • To add the analysis of the C-Reactive protein at the screening visit only • To add two timepoints assessments for the microbiote at Day 65 and Day 125 visits and explain the optional analysis of the post treatment assessments.
V.4.0, 07SEPT2016, Amendment #2	See rationale for Protocol amendment #2 (above)

LIST OF DEFINITIONS AND ABBREVIATIONS

DEFINITIONS

Audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analysed, and accurately reported according to the protocol, Sponsor's standard operating procedures, good clinical practices, and the applicable regulatory requirement(s).
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the study-related requirements, good clinical practices (GCP) requirements and the applicable regulatory requirements.
End of Study	End of study (study) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active subject in the study.
Enrol / Randomise	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
Enter/Consent	The act of obtaining informed consent for participation in a clinical study from subjects deemed- or potentially eligible to participate in the clinical study. Subjects entered into a study are those who sign the informed consent document directly or through their legally acceptable representatives.
Ethics Committee	A board or committee (institutional, regional, or national) composed of medical professional and non-medical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical study are protected.
Investigator	A Physician responsible for the conduct of a clinical study at a study site. If a study is conducted by a team of individuals at a study site, the Investigator is the responsible leader of the team and may be called the principal Investigator.
Preliminary (interim) analysis	Any analysis intended at any time prior to the formal completion of a study.
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves [invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws)]. For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
Subject	An individual who is or becomes a participant in clinical research, either as a recipient of the test article or as a control. A subject may be ether a healthy human or a patient.

ABBREVIATION	
A1C	Haemoglobin A1c
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the (plasma concentration vs. time) curve
AUC0-∞	Area under the (plasma concentration vs. time) curve from time 0 to infinity
AUC0-X	Area under the (plasma concentration vs. time) curve from 0 to time X
AUCt	Area under the serum concentration time curve from time 0 to last quantifiable timepoint
Beta HCG	Beta Human Chorionic Gonadotrophin
BLL	Blood Lead Level
BMI	Body mass index
CA	Competent Authorities
CFD	Chronic functional diarrhoea
Cl	Clearance
Cl/F	Apparent total clearance (from plasma)
CKD-EPI	Chronic Kidney Disease Epidemiology collaboration
C_{max}	Observed maximal (peak) concentration
C_{min}	Observed minimum concentration
$C_{Through}$	Concentration at the end of the dosing interval
CMC-SC	Chemistry Manufacturing and Control- Supply Chain
CRF	Case report form: a printed or electronic form for recording study subjects' data during a clinical study, as required by the protocol.
CRO	Contract research organisation
CRU	Clinical research unit
CV	Coefficient of variance
DBP	Diastolic Blood Pressure
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ED	Early Discontinuation
EMA	European Medicines Agency
EoS	End of Study
FDA	Food and Drug Administration
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GMP	Good manufacturing practices
HCG	Human chorionic gonadotrophin

ABBREVIATION	
HIV	Human immunodeficiency virus
HR	Heart rate
IAD	Interim access to data
IBS	Irritable bowel syndrome
ICH	International conference on harmonisation
ICP-MS	Inductively coupled plasma- mass spectrometry
IEC	Independent Ethic Committee
IHMS	International Human Microbiome Standards
IRB	Independent Review Board
IMP	Investigational Medicine Product
MAH	Marketing Authorisation Holder
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NCA	Non-compartmental approach
ND	Not done
ORS	Oral rehydration solution
PBRER	Periodic Benefit-Risk Evaluation Report
PDE	Permitted daily exposure
PDM	Pharmacokinetics and Drug Metabolism
PK	Pharmacokinetic
PSUR	Periodic Safety Updated Report
SAE	Serious Adverse Events
SBP	Systolic blood pressure
SD	Standard deviation
SmPC	Summary of Product Characteristics
SNSPE	Système National de Surveillance de Plombémie chez l'Enfant
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
t_{max}	Time of observed C_{max}
TEAE	Treatment Emergent Adverse Event
TID	Three times a day
TMF	Trial master file
V	Volume of distribution
ULL	Urinary lead level
WHO	World Health Organisation

1 STUDY DRUG BACKGROUND INFORMATION

1.1 Investigational Medicinal Product Name

Diosmectite is a natural clay belonging to the dioctahedral smectite family extracted from monospecific geological deposits specially selected for their high quality.

These clay minerals present a complex and stable crystallographic structure which is characterised by units made up of tetrahedral silica sheets alternating with sheets in which aluminium and magnesium are embedded in an octahedral coordination, strongly binding these atoms to the lattice. The conversion of the crude clay into the active pharmaceutical ingredient requires a complex and long multi-step process to purify and remove impurities in order to yield an off-white to slightly beige, tasteless and odourless, stable, very fine powder with consistently high quality.

Diosmectite is an anti-diarrhoeal gastro-intestinal protectant. Thanks to its leaflet structure and high plastic viscosity, diosmectite has a powerful coating property on the gastrointestinal mucosa.

Pharmacological studies reveal that diosmectite:

- acts as mucus stabiliser and cytoprotector for gastrointestinal mucosa against aggressive agents such as hydrochloric acid, biliary acids salts, and other irritants,
- exhibits a high adsorption capacity against enterotoxins, bacteria and virus,
- reinforces intestinal mucosa barrier,
- restores the epithelial barrier defect induced by the proinflammatory cytokine TNF-α (involved in several intestinal disorders: infectious diarrhoea, inflammatory bowel diseases and food allergy).

Diosmectite is marketed in more than 70 countries for the following indications: the treatment of acute diarrhoea in children (including infants) in association with oral rehydration solution (ORS), the treatment of acute diarrhoea in adults, the symptomatic treatment of chronic functional diarrhoea in adults and the symptomatic treatment of pain associated with functional bowel diseases in adults.

For this study diosmectite will be provided as Smecta® Orange-vanilla (as flavouring agents) and supplied as sachet of powder for oral suspension; each sachet contains 3 g of diosmectite, in the form dioctahedral diosmectite, as active ingredient.

1.2 Findings from Nonclinical and Clinical Studies

Reference information about diosmectite can be found in the Summary of Product Characteristics (SmPC) of Smecta® as approved in France.

In addition to multiple clinical studies performed in acute diarrhoea with Smecta®, clinical studies after chronic administrations of Smecta® have been performed in patients with chronic functional diarrhoea (CFD) and in patients with diarrhoea-predominant irritable bowel syndrome (IBS subtype D), according to the Rome II/III Classification (Yao-Zong Y et al., 2004, Chang FY et al. 2007, Dumitrascu DL et al. 2004). In these studies, the administration of Smecta® was from 2 to 8 weeks with administration of Smecta® three times a day (TID). The clinical documentation of Smecta® has been updated regularly for periodic review, the Marketing Authorisation Holder (MAH) re-evaluate the data supporting the efficacy claims for Smecta®. In parallel, the risk and benefit of Smecta® has been regularly reviewed through Periodic Safety Update Reports (PSURs) and Periodic Benefit-Risk Evaluation Reports (PBRERs) which concluded that the benefit risk ratio for the compound in this current indication is favourable.

1.3 Known and Potential Risks

From the incidence rates in clinical trials, the most commonly expected adverse drug reactions (ADR) following Smecta® administration is constipation, occurring in approximately 7% of adults. After administration of Smecta®, rash and urticaria have been observed as uncommon and rare ADRs, respectively.

Additional information regarding risks and benefits after the administration of Smecta® to human subjects may be found in the SmPC of the product.

1.4 Selection of Investigational Medicinal Product Dose and Dose Regimen

The dose strength of Smecta® 3g TID corresponds to the approved dose for the treatment of chronic diarrhoea in adults.

Typically, chronic diarrhoea is defined as watery or loose stools that last for at least four weeks. Therefore, the duration of 5 weeks of treatment with Smecta® has been selected based on the likely minimum duration of a repeated chronic treatment course in patients with functional chronic diarrhoea. This is further supported by consumer health data collected by the MAH.

1.5 Study Population

Adult subjects with functional chronic diarrhoea will be enrolled in this study as they represent one of the most representative target patient population for Smecta® according to its indications and requiring repeated chronic administrations.

1.6 Potential Benefits to Participants

Since the study participants will be required to collect repeated blood and urine samples and stop their study treatment for 3 months during the follow up, this study has to be considered as a study without a direct therapeutic benefit resulting from their participation in this study. However subjects enrolled in this study should be improved by Smecta® for their symptoms related to their chronic functional diarrhoea during the study treatment period.

1.7 Rationale for the Study

The recent ICH guideline on elemental impurities (ICH Q3D, step 4, 2014) imposes to perform a risk assessment on medicinal products containing elemental impurities. These elemental impurities consist in particular in cadmium, lead, arsenic, mercury, cobalt, vanadium, nickel, that may be present in natural constituents of mineral origins such as diosmectite extracted from a quarry.

These elemental impurities have been categorised in ICH Q3D guidelines into 3 classes (refer to Attachment #5_Section 15.5) based on their toxicity (based on a permitted daily exposure (PDE)) and likelihood of occurrence in the drug product.

For other elements such as aluminium, manganese or zinc no limiting PDE has been established yet.

Lead has been identified as the major elemental impurity in Smecta®; indeed, in case of chronic diarrhoea posology i.e. 3 sachets of diosmectite (Smecta®) or 9 g per day, the lead intake could be a total amount of approximately 46.35 µg/day. This amount exceed the amount allowed by the new upcoming ICH Q3D guideline which comes in force for existing marketed drug in December 2017, and that will limit the lead ingestion PDE to 5 µg/day.

The amount of other Class I elemental impurities contained in 3 sachets of diosmectite (Smecta®) such as arsenic and barium are approximately 4.23 µg/day and 1395 µg/day respectively and thus below their respective new PDE (15 µg/day for arsenic and 1460 µg/day for barium).

In vitro studies aiming at reproducing the gastrointestinal environment, have evidenced lead and other elements delivery from clay in acid pH, and reintegration of the elements in the clay sheets in basic pH environment. Experimental studies in animal models for assessing the bioavailability and absorption of elemental impurities have not been evaluated as predictive of human exposure.

However, how much of this lead could be bioavailable for potential stomach and intestine absorption in adult patients after chronic oral ingestion of Smecta® is unknown as well as the absorption of these elemental impurities.

From more than 40 years of sales of Smecta®, no adverse events potentially related to elemental impurities, particularly saturnism and/or chronic lead intoxication symptoms have been reported to Ipsen or to Health Authorities. In addition, no signal within the Ipsen Pharmacovigilance Safety Data Base, and notably in targeted body systems (such as nervous system, blood and lymphatic, renal and urinary), has been detected.

Furthermore, declaration of lead intoxication is mandatory in France. Between 1995 and 2014, neither lead intoxication, nor blood lead level > 100µg/l have been reported in children taking Smecta® to the SNSPE (Système National de Surveillance de Plombémie chez l'Enfant).

However, regarding the new ICHQ3D guidelines, Smecta® does not comply with the new requirements. Therefore, the MAH considered that in order to perform an appropriate risk assessment of elemental impurities contained in Smecta®, including lead as primary elemental constituent, clinical data need to be generated in humans after chronic administration of Smecta®.

Lead is a common element found in low concentration in the Earth's crust. It is widely used in industry, particularly in products such as construction materials, paint, batteries and piping. Lead causes health problems such as toxicity of the liver, kidneys, hematopoietic system and nervous system. During the 70's and 80's, concern over lead related health problems led to the introduction of unleaded gasoline and the banning of lead based paint (for review see Kim et al. 2015). After lead enters the body, it can transit along several pathways depending on its source (organic or inorganic). The fraction of lead that is absorbed depend mainly on the physical and chemical form. Other important factors are subject's specific such as age, gender, smoking and nutritional status. The half-life of lead in the blood compartment is about 40 days in adults (99% of circulating lead is contained in the erythrocytes, Rabinowitz, 1991). The half-life of lead in blood of children and in pregnant women is reported to be longer due to bone remodelling. Residence time in other organs such as bone is much longer and ranges from 10 to 30 years. Whole blood and serum/plasma have been used as biological fluid used for the assessment of lead exposure both for screening, bio-monitoring and diagnostic purposes (Barbosa F et al. 2005, Falq et al. 2011).

Blood lead level (BLL) from whole blood is the main biomarker used to monitor exposure and has been widely used in numerous epidemiological studies. BLL is a balance between recent absorption of lead and a removal of lead stored in the body, especially in bone (Christoffersson et al., 1986; Nilsson et al., 1991) and is representative of the internal dose of lead in the organism when the exposure is stable (Barbosa et al., 2005). Plasma lead level could be a better biomarker, especially at high exposure (workers for example) (Rentschler and al, 2012 – Bergdhal and al, 1997). Reference ranges for estimation of a baseline of lead level in European Western countries are available for blood (Falq and al, 2011). Estimation of blood lead levels have been considered for the current study as the primary endpoint. In addition, it is proposed to biobank samples for potential assessment of lead levels in plasma.

The intestinal microbiota (containing about 90% of the body microorganisms) contributes to intestinal homeostasis through direct regulation of the development of the intestinal mucosa and maturation of the immune system. Therefore, the intestinal microbiota can be perceived as an integral component of the host's physiology.

An increasing number of studies emphasizes the diverse roles of the intestinal microbiota. These roles are often associated with beneficial physiological effects for the host, reflecting a symbiotic and beneficial crosstalk between cells of the intestinal epithelium and the resident microbiota. However, the cellular and molecular mechanisms developed by the microbiota in order to influence the host's intestinal cell responses remain poorly understood.

The understanding of the complex host-microbiota relationship and the possibility to modulate these interactions is of key importance for human health. Our knowledge on the various contributions of the microbiota to health is still in its infancy and the underlying cellular and molecular mechanisms of its interplay with the host intestinal cells remain poorly understood (de Wouters et al., 2014).

We would like to take the opportunity of this study to explore the potential effect of Smecta® on the microbiota by collecting selected faecal samples at various time point before, during and after the chronic administration of Smecta®.

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the concentration of lead in blood, one of the Class I elemental impurities defined by ICH Q3D guidelines, after chronic administration of Smecta® in subjects with chronic functional diarrhoea.

2.2 Secondary Objectives

- 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.

2.3 Exploratory Objectives

- An ancillary study will be conducted during this study to assess the bowel microbiote composition, stools consistency and frequency after chronic administration of Smecta® in subjects with chronic functional diarrhoea.
- Additional blood samples will be biobanked in order to further potentially assay other elemental impurities levels (see Attachment #5_Section 15.5);
- Plasma samples will be biobanked in order to further potentially assay lead in plasma.

3 INVESTIGATIONAL PLAN

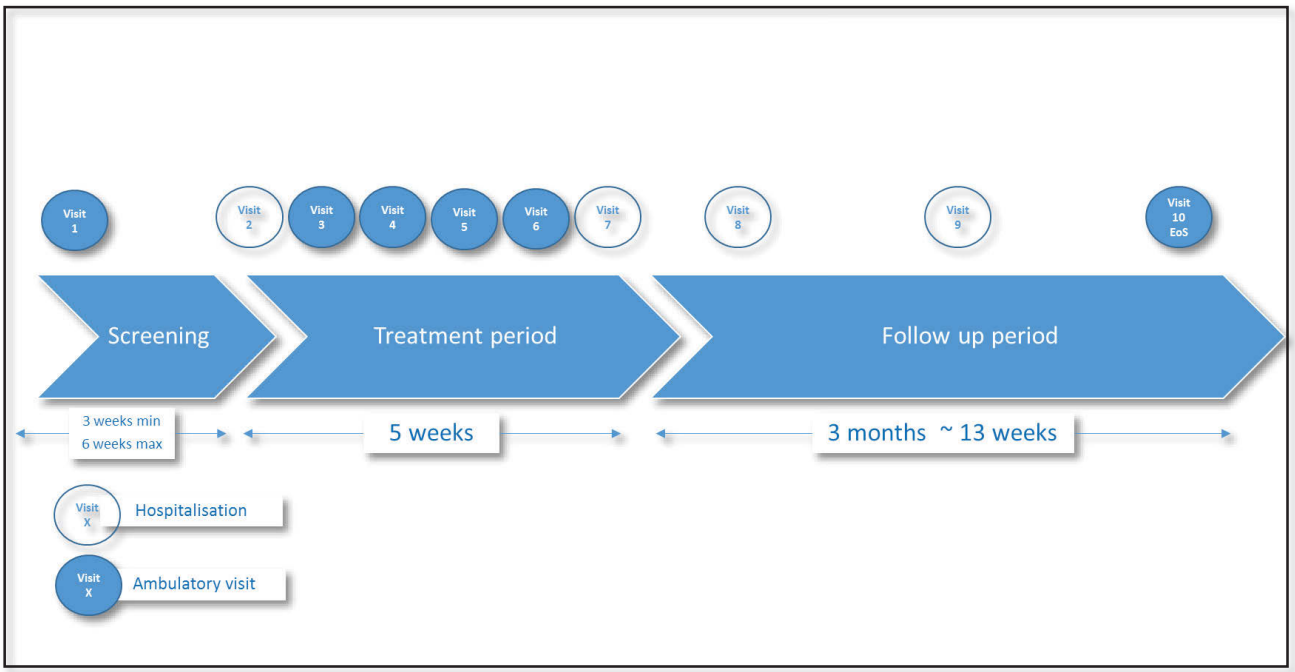
3.1 Overall Study Design

This is a prospective, open-label, non-comparative, multi-centre, international, without direct individual benefit study, assessing the potential absorption of elemental impurities after chronic administration of Smecta® in subjects with chronic functional diarrhoea. It is intended that a total of 35 subjects will be enrolled (i.e. assigned to a treatment, please see section 4.1) to ensure that at least 29 subjects will complete the study. It is planned to have at least 40% of each gender in the entire study.

After a screening period of up to 6 weeks including a baseline assessment, each subject will be dosed with Smecta® 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 (see Figure 1). Blood samples, urine collections and faecessampling 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.

No formal interim analysis is planned during the study. However, BLL obtained on screening and baseline (prior the first intake of Investigational Medicine Product (IMP)) and during the study will be analysed and reviewed on an ongoing basis by the Sponsor for potential study adjustments (e.g.: confirm assumptions for sample size calculation).

Figure 1 Study Design and Visits



3.2 Primary and Secondary Endpoints and Evaluations

Concentration of lead, other elemental impurities and other endpoints assessed in this study are further described below.

3.2.1 Pharmacokinetics of Lead, other Impurities Endpoints and Evaluations Methods

Primary Endpoints:

Changes in BLL from baseline during treatment and post-treatment follow-up period. PK parameters of lead may be calculated if feasible.

Secondary endpoints:

- Change from baseline of concentrations of other selected Class I elemental impurities (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.
  PK parameters of selected Class I and Class IIa impurities may be calculated if feasible.
- 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.

3.2.2 Exploratory Endpoints

3.2.2.1 Microbiote assessment

Microbiote characteristics will be evaluated during Smecta® treatment and follow up and compared to baseline.

The method of samples and dosing will be detailed in a separated technical document developed in collaboration with Institut National de la Recherche Agronomique (INRA) – Jouy-en-Josas, France.

Consistency of stools (recorded and rated according to Bristol scale) (See Attachment #7_Section 15.7) and frequency will be assessed over 24h by the subject as described in the Study Schedule (See Attachment #1_Section 15.1).

3.2.2.2 Biobank

Blood and urine samples will be stored for potential further dosages of other elemental impurities as lithium (Li), antimony (Sb), molybdenium (Mo), copper (Cu), Tin (Sn) and chromium (Cr).

Plasma samples will be biobanked in order to further potentially assay lead in plasma. If feasible, PK modelling of lead (and potentially other elemental impurities levels) may be performed.

3.2.3 Safety Endpoints and Evaluations

Safety Endpoints will be assessed as described in the Schedule of events (see in Attachment #1_Section 15.1):

- physical examination, vital signs, ECG,
- clinical laboratory blood tests (see in Attachment #2_Section 15.2),
- Adverse Events and Treatment Emergent Adverse Events (TEAE).

To note: During the study additional assessments may be performed at the discretion of the Investigator in case of adverse events.

3.3 Subjects Managements

3.3.1 Study Visits and Procedures

Study visits and procedures are described in the Study Schedule of Events (see Attachment #1_Section 15.1).

It is planned that subjects will be resident in the Clinical Research Unit (CRU) at particular study visits, mainly during 24-hour urine collection. Otherwise, subjects will self-administer and come to the CRU at regular interval for drug supply, blood and urine collections as well

as the review of adverse event as described below in this section and in the schedule of events (see Attachment #1_Section 15.1).

Compliance to diosmectite (Smecta®) intake will be monitored through the use of subject diary.

3.3.1.1 Screening Period

The subjects will attend the CRU (Visit 1) to enter the screening period within 21 to 42 days prior to dosing Visit 2.

After a subject has been checked for pre selection criteria, has received complete explanations and response(s) to his/her potential questions about the study by the Investigator (or designee) and has been given reasonable time to think about it, a signed and dated informed consent form will be obtained prior to any study procedures.

Once informed consent is obtained, subjects will be allocated a study-specific subject number which must comply with formatting specifications provided by the Sponsor.

Demographic data will be collected including race, smoking status, alcohol consumption, and dietary habits.

The screening tests and assessments will then be performed to check compliance with Inclusion/Exclusion criteria and study restrictions. The results must be obtained and confirm subject's eligibility prior to dosing on Visit 2 at Day 1.

3.3.1.2 Baseline

The subjects will come back for admission to the CRU (Visit 2), 3 to 6 weeks later at the latest on Day -1 in the morning, at the discretion of the Investigator, to be resident in the CRU for obtaining a 24-hour urine collection as well as stool sample(s) for baseline evaluation. Based on Investigator judgement or if required locally, some of the screening assessments may be redone to confirm that subjects are still compliant with the Inclusion/Exclusion criteria and study restrictions.

3.3.1.3 Treatment Period

The treatment period will occur from Day 1 (first intake in the morning) to Day 35 (last intake in the evening) and subjects will be required to attend the CRU on several occasions during the treatment period:

- Day 1 (Visit 2): The subjects will be dosed within the unit with Smecta® at breakfast, lunch and dinner time, PK samples will be collected as described in the Schedule of events (see Attachment #1_Section 15.1) and the subject will leave the unit on Day 2 after PK sampling and Smecta® administration in the morning. Subjects will receive a box containing Smecta® treatment for a bit more than 2 weeks (20 days) as well as a diary to record the drug administration and consistency and frequency of stools at the day before the Day 8 visit.
- Out-patient visits (Visits 3 to 6): the subjects will be required to come back to the CRU for out-patient visits on Days 8, 15, 22 and 29 for blood sampling for impurities dosing and the review of adverse events and concomitant medication. One day before Day 8, subject will need to complete the diary with assessment of consistency and frequency of stools using the Bristol scale. During those visits, stools will be collected only on Day 8. At Day 22 the subjects will receive a second box containing Smecta® treatment for the last 2 weeks.
- Days 35-36 (Visit 7): Subjects will come back to the CRU in the morning of Day 35 (or the evening before for convenience) in order to start the process to collect urine samples, blood and stools sampling. They will be dosed with Smecta® at breakfast,

lunch and dinner. They will leave the unit in the morning of Day 36 after the completion of the 24-hour urine collection and PK sample in the morning.

3.3.1.4 Post-Treatment Period

The subjects will be asked to come back to the CRU at two occasions during the post-treatment period: these visits should occur at Week 9 (Visit 8) and at Week 13 (Visit 9). At Visit 8 and 9, blood sampling will be collected as well as 24-hour urine collection for impurities dosing. Stools samples will be collected only at Visit 8 (week 9) and Visit 9 (Week 13).

3.3.1.5 End-of-Study (EoS)/Early Discontinuation Visit (ED) (Visit 10)

Subjects will be discharged from the study after completion of the EoS visit for follow-up assessments as described in the Schedule of event (see Attachment #1_Section 15.1) which will happen approximately 4 weeks after Visit 9, or earlier in case of early discontinuation.

3.3.2 Subjects Disposition

All subjects visits will be out-patient, except for Visit 2 (Day -1 to Day 2), Visit 7 (Day 35 to Day 36) and Visits 8 and 9 (where subjects will be hospitalized in the CRU). For convenience, subjects may come the evening before the hospitalisation as study assessments start early morning.

3.3.3 Study Duration

For each individual subject, the study is expected to last approximately 5,5 months, including up to 42 days for screening assessments, 35 days of treatment and a 3-month post-treatment follow-up period.

3.4 Study Conduct

It is planned to dose the subjects based on enrolment capabilities of each Clinical Research Units (CRU) and to limit as much as possible the number of cohorts. As there are no safety concerns or limitation with the administration of study drug, multiple subjects may be dosed at the same interval. The recruitment of subjects will be competitive between the CRUs.

3.5 Rationale for the Study Design

Discussion of Design

The primary objective of the study is to investigate the Blood Lead Levels after the chronic oral administration of Smecta® in subjects suffering from chronic functional diarrhoea. In each subject, lead concentrations obtained at several occasions during and after dosing with Smecta® will be compared to each individual baseline data. Other elemental impurities levels will be assessed in blood comparatively to baseline. Moreover, 24h urine level of all these impurities will be collected and assessed by mean of validated analytical methods. Samples of biobanking will be collected for potential other elemental impurities assessments as well as the potential measurement of lead in plasma. Stools samples and the assessment of stool consistency and stool frequency will be also collected for microbiote assessment as ancillary study.

Considering the extensive distribution of lead in the body as well as its long term residence time, a post-treatment follow-up period of 3-months has been considered appropriate to detect any change in the elemental impurities within the frame of a chronic administration of Smecta®.

Dose Selection and Dosing Regimen

The dose of Diosmectite (i.e. 1 sachet (3g) TID) is the recommended dose for Smecta® in the indication of chronic diarrhoea in an adult population.

For the purpose of this study, and in order to potentially limit variability and increase the bioavailability of lead (higher at low pH) dosing of Smecta® will occur in condition of fast 30 minutes before breakfast, 1 hour before noon lunch and 1 hour before evening dinner.

Five (5) weeks can be considered as a repeated chronic administration as chronic diarrhoea is defined as usually lasting more than 4 weeks.

Population Selection and Sample Size

The targeted subject population to assess the primary endpoint are subjects with chronic functional diarrhoea, one of the indication of Smecta® with subjects treated daily for several weeks.

Indeed, lead absorption could be different in subjects with normal gastro-intestinal transit time from patients with various gastrointestinal disorders of organic origin. Moreover patient with acute diarrhoea require a treatment lasting usually for 3 to 7 days that is far from chronic condition.

Important factors, that impact the fraction of lead that is absorbed, may depend on the subject's age, gender, smoking, fasting and nutritional status (Falq et al. 2011); this is why the subjects above 60 years of age will not be included in the study. Smoking and nutritional status will be part of the demographic data collected in this study. Smecta intake and fasting status will be standardized as far as possible. To have approximately equal representation in each gender, 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).

See Section 8.1.2 for sample size determination.

4 POPULATION RECRUITMENT, ENROLMENT AND WITHDRAWAL

4.1 Definitions

Screened Subject:

A screened subject is a subject who correspond to the preselection criteria, who signed the Informed Consent and could potentially be enrolled into the study.

Screening Failure:

A subject is considered as a screening failure when he/she is not enrolled in the study after signing the Informed Consent.

Subject Enrolment:

A subject is considered as enrolled in the study when he/she is assigned to a treatment.

Subject Drop-out:

A subject will be considered as drop-out when, for any reason, he/she withdraws from the study or is discontinued from the study after enrolment.

4.2 Recruitment of Population

As described in Section 3.3.1, subjects will be screened within 42 days before dosing on a free voluntary basis. The criteria for enrolment must be followed explicitly. If a subject who does not meet enrolment criteria is inadvertently enrolled, he/she should be discontinued from the study and the Sponsor or its designee must be contacted.

As illustrated in the Study Schedule of Events (see Section 15.1), eligibility of subjects in the study will be based on the results of a screening medical history (including any pre-existing conditions, and previous/concomitant medication(s)), physical examination, clinical laboratory tests, vital signs and electrocardiogram (ECG). These tests / assessments may be performed at any time during the screening period (Day -42 to Day -21, included) after

Informed Consent signature. Results of tests and assessments required at screening should be available to confirm subject's eligibility prior to first dosing on Day 1.

4.3 Inclusion Criteria

Potential study subjects may be entered in the study if they meet all of the following criteria:

(1) Provision of written informed consent prior to any study related procedure.

(2) Male or female subjects aged between 18 and 60 years (inclusive) at the time of giving informed consent.

(3) Subjects with chronic functional diarrhoea defined as "Loose (mushy) or watery stools according to Bristol scale grade 6 and 7, occurring in at least 75% of stools for the last 3 months with symptoms onset at least 6 months before diagnosis, without or with pain (including Irritable Bowel Syndrome)" as documented in subject's medical history.

(4) Body Mass Index (BMI) between 19 and 32 kg/m^2 (inclusive), with minimum body weight of 50 kg, at screening.

4.4 Exclusion Criteria

Potential study subjects may not be entered into the study if any of the following apply:

Exclusion criteria related to the disease:

(1) Identified or strongly suspected organic cause to diarrhoea, e.g. ulcerative colitis, Crohn's disease, Celiac disease, bowel malabsorption, chronic pancreatitis, chronic diarrhoea primarily due to diabetes.

(2) Any drug induced diarrhoea.

Exclusion criteria related to the study drug:

(3) Prior exposure to diosmectite or other clay(s) or charcoal or other compounds of mineral origin e.g. talc, kaolin, etc. within 1 month prior to screening.

(4) Except the administration of Smecta® as part of the study treatment, subject should not self-administer any other diosmectite, including Smecta or other clays or charcoal or other compounds of mineral origin during the study..

(5) History of any serious adverse reaction or adverse event or hypersensitivity to any component of Smecta®.

(6) Active lactose and/or fructose Intolerance, deficit in sucrose/maltase or glucose malabsorption as documented in subject's medical history.

(7) Repeated daily intake of drugs with narrow therapeutic index margin (e.g. digoxin, theophylin) (see list in Attachment #4_Section 15.4).

Exclusion criteria related to primary end point:

(8) Known domestic, leisure or professional exposure to elemental impurities, notably lead, arsenic, cadmium, mercury, aluminium as e.g. building workers, metallurgy, auto repairers, scrap metal recyclers, painting, pottery, shooting (see complete list in Attachment #6_Section 15.6).

(9) Artificial feeding.

(10) Subjects eating shellfish (crustaceans, molluscs) more than 2 times a week.

(11) Subjects living in an old building or house using materials containing lead.

(12) Planned changes either of residency or of professional/leisure activities during the study (including follow-up period) that may increase the likely exposure to elemental impurities.

Exclusion criteria related to the ancillary study on digestive microbiota:

(13) Antibiotic agent intake within the month prior to baseline visit (Day -1).

(14) Risk of antibiotic treatment course during the study.

(15) Need for metformin and or proton pump inhibitors (PPI) intake within the month prior to baseline or during the study.

Other Exclusion criteria related to the study protocol:

(16) Receipt of any investigational agent or study drug within 3 months prior to screening.

(17) Presence of clinically significant physical, laboratory, vital signs, or ECG findings that, in the opinion of the Investigator, Medical Monitor, and/or the Sponsor, may interfere with any aspect of study conduct or interpretation of the results.

(18) History of any major surgery within 6 months prior to screening or anticipated surgery during the study.

(19) Women who are breastfeeding or are planning to become pregnant during the study,

(20) Positive pregnancy test at screening or baseline.

(21) Loss or donation of blood >500 ml within 3 months before screening, and/or going to donate blood during the study.

(22) Poor venous access as defined by the Investigator or designee.

(23) Positive for hepatitis B antigen or hepatitis C virus.

(24) Positive results for human immunodeficiency virus, or had received diagnosis for acquired immunodeficiency syndrome.

(25) No history or clinically significant symptoms or severe disease, including cardiac, neurological, pulmonary, hepatic, biliary, gastrointestinal, endocrinologic, or renal disorders, or cancer within the last 5 years (except localised or in situ cancer of the skin and cervical cancer in situ).

(26) Need for special dietary restrictions, unless the restrictions are approved by the Investigator.

(27) Likely to be uncompliant or uncooperative during the study, in the judgment of the Investigator.

(28) Unable to understand the nature, scope and possible consequences of the study, in the judgment of the Investigator.

(29) Any known factor, condition, or disease that might interfere with treatment compliance or study conduct such as drug or alcohol dependence or psychiatric disease.

(30) Sponsor employees or Investigator site personnel directly affiliated with this study, and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

4.5 Randomisation

No randomisation list will be required for this open-label, non-comparative study. Subjects will be identified throughout the study with the subject number assigned at enrolment.

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).

4.6 Discontinuation of an Individual Subject

4.6.1 Discontinuation / Withdrawal Criteria

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 violation or 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.

4.6.2 Follow-up Procedures for Drop-out Subjects

In case a subject who has already taken study medication(s) drops out or is discontinued from the study earlier than study end, he/she should follow the EoS/ED visit assessments (Visit 10) as appropriate. The reason and date for drop-out should be documented.

Drop-out subjects will have completed their study participation when they have undergone all assessments of this last study visit (EoS/ED), and electronic case report form (eCRF) should be completed up to these last assessments.

Data collected prior to subject discontinuation will be kept in study records and shared with the Sponsor for study analyses (see Section 9) unless a subject formally specifies his decision to withdraw his consent for using data already collected before discontinuation.

4.6.3 Replacement Strategy

No replacement of subjects is foreseen in the study.

4.7 Discontinuation of Study Site(s)

Study site participation may be discontinued if the Sponsor or its designee, the Investigator judges it necessary for any reason within agreed timelines per contract when enrollment of subjects has not commenced.

After the start of subjects enrollment, the study site participation may be discontinued for more restrictive reasons described in the contract (ex: request of withdrawal from local regulatory authority or the ethics committee of the study site, or for the best interests of the subjects's health, or because sponsor or it designee or the CRU has been declared insolvent or a bankruptcy/winding-up petition has been filed…). The contract signed with the CRU will be leading in case of discrepancy between the protocol and the contract.

4.8 Discontinuation of Subject's Recruitment

Subjects' recruitment in the study may be stopped at any time upon Sponsor's decision, e.g. if actual data indicate that a sufficient number of subjects have already been enrolled in the study or for any other appropriate reason.

4.9 Study Termination

The study can be discontinued prematurely if the Sponsor judges it necessary either for reasons described in Section 4.7 or for any other appropriate reason. In that case, best efforts should be made that all scheduled procedures and assessment for subjects who are still in the study will be performed.

5 STUDY TREATMENT

5.1 Study Drug and Treatment of Subjects

5.1.1 Investigational Drug Formulation

Diosmectite, marketed as Smecta®, originating from a single batch number/lot, appropriately labelled for its use in clinical trials (Annex 13 of Good Manufacturing Practices (GMP) guidelines on IMP) will be provided to the pharmacy of the CRU.

Dosage Form and Strength of Smecta®

Smecta® will be provided as sachets, each sachet containing 3 g of diosmectite as powder for oral suspension. Excipients include glucose monohydrate, saccharine sodium, orange flavour and vanilla flavour.

Supplies Manufacturing, Packaging and Release

Smecta® will be manufactured, labelled and packed as individual subject kits by Ipsen Pharma (Beaufour Ipsen Industrie (Dreux France) or its delegate who will perform secondary labelling, packaging, release and shipment to the CRUs, according to applicable regulations and guidelines.

The batch used for the study will be selected based on the maximal level of lead according to the Smecta® specification for batch release (approximately 4.7µg/g).

A Certificate of Analysis reflecting the product release statement will be issued for the batch of Smecta® used in this study, together with a Certificate of Compliance with GMP.

Labelling

The label texts for packaging units will be in compliance with Annex 13 of the European Union (EU) Guide to GMP and should be translated or adjusted to be in compliance with applicable regulatory requirements, national laws in force and local languages.

Storage

The Investigator, or designee (e.g. pharmacist), will ensure that IMPs will be stored, and returned or destroyed according to applicable regulations. The IMP will be stored at the CRU in a secured and locked area, at room temperature, in accordance with applicable regulatory requirements and any other specific instructions provided by the Sponsor.

At the CRU, supplies for this study will not be stored in such a way that they may be confounded with supplies being used for another study.

Investigational Drug Accountability

Smecta® will be provided to the Investigator, or designee (e.g. Pharmacist), and administered to subjects after appropriate instructions as described in Sections 5.1.2 and 6.1.

The Investigator or designee (e.g.: Pharmacist) will record drug movement and accountability on specific drug accountability forms/logs. Study medication allocation, preparation and disposition records, as well as shipping, dispensing and returned drug records, and inventory logs must be maintained at the investigational site.

The dispensing for each subject will also be recorded in the eCRF.

It is essential that all used and unused supplies are retained for verification by the study monitor or designee who will ensure that Smecta® administration in the eCRF, the accountability forms/logs and the number of remaining used/unused treatments are consistent.

At the end of the study after confirmation from Sponsor or its designee, all remaining IMPs will be either destroyed at the site (preferred option) or returned to CMC-SC (Beaufour Ipsen Industrie – Dreux- France) for destruction (only if site is not able to do it).

5.1.2 Study Drug Administration

The Investigator, or designee, will only dose and allocate Smecta® treatment to subjects enrolled in this study.

Two kits of Smecta® will be prepared and provided to subject(s) according to the pre-determined dosing schedule agreed upfront with the Sponsor or designee; each kit consisting of one box, containing 60 sachets of Smecta® covering the administration for 20 days.

Each subject will be instructed to ingest Smecta® at three occasions, in the morning, at noon and in the evening, and every day until the Day 35 visit included. In order to standardize the conditions of administration of Smecta® and potentially limit the variability and increase bioavailability of lead all along the trial, Smecta® should be taken in fasting and at least one hour before meal, except for breakfast at least 30 minutes before.

The actual time of dosing of all Smecta® ingestions will be recorded by the subject on his/her own Diary as well as the start and ending time of the meals, and reported by the site in the eCRF, or will be recorded by the site when applicable in the eCRF.

Subjects will be instructed to contact the Investigator as soon as possible if he/she has a complaint or problem with the study drug so that the situation can be assessed.

5.2 Blinding

Not applicable (open label study).

5.3 Product complaint

Sponsor collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

The Investigator is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- Recording a complete description of the product complaint reported and any associated adverse events (AEs) using the study-specific complaint forms provided for this purpose.
- Faxing the completed product complaint form within 24 hours to Sponsor or designee.

If the Investigator is asked to return the product for investigation, they will return a copy of the product complaint form with the product.

6 STUDY RESTRICTIONS

6.1 Study Drug Administration

The content of sachet should be reconstituted with water (approximately 200 ml), just before ingestion.

The regimen of intake is three times per day (TID) in fasting state, with consequently the following timings:

- at wake up time , at least 30 minutes before breakfast
- in the morning, 1 hour before lunch time
- in the late afternoon, 1 hour before dinner time

Example : if breakfast at 7:30, lunch at 12:30 and dinner at 19:30,

Smecta® intake should occur :

- at wake up time and before 7:00
- in the morning at 11:30
- in the late afternoon at 18:30

If a dose administration is missed, subject is instructed to ingest the missing dose together with the next dosing occasion. If no meal at a given day is taken (e.g. breakfast), Smecta® should be taken in fasting state anyway and at three occasions (see Section 5.1.2).

6.2 Concomitant Therapy(ies)

Any other treatment should be taken at least 2 hours before or after the ingestion of Smecta®.

Drugs with a low therapeutic index are specifically excluded (e.g. digoxin, theophylline) if repeated daily intake is needed.

Antibiotics are forbidden during the study as they could interfere with microbiote evaluation.

Compounds containing Diosmectite or similar compounds or mine extracts, as well as other compounds containing elemental impurities such as antacids (e.g. Maalox) are excluded.

The list of excluded concomitant medications are listed in Attachment #4_Section 15.4.

During the study the Investigator should check if the subject has received any concomitant medication/therapy that is not permitted at study entry.

Subjects will provide information about all previous medication taken over the last month and investigational drug taken over the last 3 months, and medication taken during the study, and this information will be recorded on the appropriate eCRF.

Contraception

No specific contraception methods are required for the study participation. A pregnancy test will be performed on screening, baseline and end-of-study visit. Women are requested to be non pregnant at inclusion and not becoming pregnant during the treatment phase of the study.

Rescue Medication

Loperamide will be allowed as rescue medication should the chronic diarrhoea worsen during the study.

The recommended dose regimen will follow the SmPC of loperamide with a maximum daily dose not exceeding 12 mg.

6.3 Lifestyle Restrictions

It is requested that subject refrains from eating shellfish (crustaceans, molluscs), participate in shooting or hunting activities on a regular basis, as well as doing pottery (see Exclusion criteria).

Subjects will be asked to comply with internal CRU rules regarding smoking or other potential restrictions when resident in the CRU (see Study Schedule in Attachment #1_Section15.1).

7 STUDY ASSESSMENTS

Timing of blood lead sampling and urine collections, safety assessments and any other tests is specified in the attached study schedule of events table. Maximum blood volume for all tests and assays is also documented for each of the tests in the attached summary of blood collection volumes (See Attachment 3_Section15.3).

7.1 Safety Assessments

The Investigator is responsible for monitoring the safety of the subjects who have entered the study and to take appropriate action during the study concerning any event that seems unusual, as well as to alert the Sponsor or its assigned representative.

The Investigator remains responsible for following, through an appropriate health care option, AEs that are serious or that caused the subject to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the Investigator.

The Investigator will be responsible for a clinical assessment of the study participants before discharge from the study, and for the set-up of a discharge plan if needed.

The Sponsor Medical Monitor and the Global Patient Safety Physician will monitor safety data throughout the course of the study.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical study records throughout the study.

Safety Parameters

The following safety parameters will be collected during this study at specific time points described in the study schedule of events:

- Adverse events;
- Physical examination with aural/body temperature and body weight/height
- Vital signs, including heart rate, systolic and diastolic blood pressure;
- 12-Lead electrocardiogram (ECG);
- Clinical safety laboratories, including clinical chemistry, haematology, and urinalysis.

Further routine medical assessments or any additional safety procedures may be performed during the study, if warranted and agreed upon between the Sponsor and Investigator, or when clinically indicated.

Any clinically significant findings that result in a diagnosis should be recorded and commented on appropriate document.

7.1.1 Adverse Events

7.1.1.1 Definition

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, ECG).

An AE can include an undesirable medical condition occurring at any time, even if no IMP has been administered.

This definition includes events occurring from the time of the subject giving informed consent until the EoS/ED.

7.1.1.2 Adverse Event Collection

AEs will be monitored from the time that a subject gives informed consent and throughout the study, and will be elicited by direct, nonleading questioning or by spontaneous reports.

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

Laboratory Test Abnormalities

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

- They result in a change in IMP schedule of administration (change in dosage, delay in administration, IMP discontinuation),
- They require intervention or a diagnosis evaluation to assess the risk to the subject,
- They are considered as clinically significant by the Investigator.

Abnormal Physical Examination Findings

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

Other Investigation Abnormal Findings

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

7.1.1.3 Adverse Events Assessment

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e. IMP or other illness). The Investigator is required to assess causality and record that assessment in the eCRF.

Adverse events will be classified by the Investigator as mild, moderate or severe according to the following criteria:

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

If in the duration of an AE there is a change in intensity, each change will be recorded as a new episode of the AE.

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

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

The expectedness of an AE shall be determined by the Sponsor according to the current version of SmPC.

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

If a subject's treatment is discontinued or changed as a result of an AE, study site personnel must clearly report to the Sponsor or its designee the circumstances and data leading to such decision.

7.1.1.4 Adverse Event Follow-up

If an AE is still present at the end of the study, reasonable follow-up clinical monitoring (and up to 30 days after the end of the study) should be managed by the Investigator or any appropriate Physician until event is resolved or stabilised at an acceptable level, as judged by the Investigator. The frequency of follow-up evaluation is left to his/her discretion.

7.1.1.5 Clinical Evaluation of Safety

All study drug and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarised using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with study drug as perceived by the Investigator. Symptoms reported to occur prior to dosing will be distinguished from those reported as new or increased in severity during or after IMP administration. Each symptom will be classified by the most suitable term from a version of a medical regulatory dictionary agreed by the Sponsor and other parties involved in the study.

7.1.1.6 Serious Adverse Event Assessment

Definition

A Serious Adverse Event (SAE) is defined as any adverse event that either:

(1) Results in death,

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

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

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

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

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

(7) Other medically important conditions

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

- Hospitalisation is defined as any in-patient admission (even if less than 24 hours). For chronic or long term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.

- Prolongation of hospitalisation is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, as determined by the Investigator or treating Physician. For protocol-specified hospitalisation in clinical studies, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment emergent, clinical AE (i.e. not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject to immediate reporting to the Sponsor.

Preplanned or elective treatments/surgical procedures should be noted in the subject's screening documentation. Hospitalisation for a preplanned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

SAE Collection and Reporting

Study site personnel must immediately (within 24 hours) alert the Sponsor's pharmacovigilance contact specified on the front page of the current document of any SAE, independent of the circumstances, suspected cause or Investigator's opinion of causality, as soon as it occurs or comes to the attention of the Investigator at any time during the study period.

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

Any appropriate way of notification may be used. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

The following information is the minimum that must be provided to the Sponsor's pharmacovigilance contact:

- Study number,
- Investigational site identification,
- Subject number,
- AE,
- Investigator's name and contact details.

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

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

7.1.1.7 Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in SmPC and that the Investigator identifies as related to IMP or procedure.

7.1.1.8 Pregnancy

Pregnancy tests will be performed in all female subjects of childbearing potential as specified in the schedule of assessments (See Attachment #1_ Section15.1).

Information regarding pregnancies with a conception date either during the study period or within 6 months after dosing must be collected and reported to the Sponsor via a Standard

Pregnancy Outcome Report Form. The Sponsor will request further information from the Investigator as to the course and outcome of the pregnancy. Adverse consequences of a pregnancy will be regarded as SAEs.

The Investigator must instruct all female subjects to inform him/her immediately should they become pregnant.

7.1.1.9 Death

All AEs resulting in death either during the study period or within 6 months after dosing must be reported as a SAE.

The convention for recording death is as follows:

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

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

7.1.1.10 Reporting to Competent Authorities, IECs/IRBs and other Investigators

The Sponsor will ensure that processes are in place for submission of reports of SUSARs occurring during the study to the CAs, Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) and other Investigators concerned by the IMP.

Reporting will be done in accordance with the applicable regulatory requirements. The Sponsor must report all SUSARs to EMA's EudraVigilance database within 15 days.

Fatal and life-threatening SUSARs should be reported within 7 calendar days, with another 8 days for completion of the report.

The Sponsor can prepare additional reports for other authorities (e.g. FDA).

7.1.2 Physical Examination

Physical examinations (including body weight (in light clothes and without shoes) and height measurements will be evaluated at screening and end-of-study visit (see Study Schedule of Events, Section 15.1).

Clinically significant changes, in the judgement of the Investigator, in physical examination findings will be recorded 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.

7.1.3 Vital Signs Assessments

After 5 min of rest, supine systolic and diastolic blood pressure (SBP & DBP), heart rate (HR) and body temperature (aural) will be assessed at screening and end-of-study visit (see Study Schedule of Events, Attachment #1_Section 15.1). In case of adverse events, additional vital signs assessments may be performed at the discretion of the Investigator.

7.1.4 Electrocardiograms Assessments

Twelve-lead computerised standard ECGs, with paper printout, will be obtained while subject is in resting supine position for at least 5 minutes and until four regular consecutive complexes are available, at screening and end-of-study (see Study Schedule of Events, Attachment #1_Section 15.1). In case of adverse events, additional ECG assessments may be performed at the discretion of the Investigator.

For each timepoint, computerised standard ECGs will be recorded so that the following parameter can be automatically calculated and reported on the ECG paper printout:

- Sinus rhythm,
- RR interval duration or heart rate (HR),
- PR interval duration,
- QRS interval duration,
- QT interval duration,
- QT interval corrected by the appropriate correction method (e.g.: Bazett).

Automated ECG interval data will be interpreted by a qualified Physician at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present. The qualified Physician will document his/her review and interpretation (including evaluation of clinical significance in case of abnormality) on every ECG printout.

The paper printouts will be kept in the source documents at site. Only the interpretation and abnormalities will be reported in the eCRFs for integration with other clinical study data. These paper ECGs may be subject to further review, if appropriate.

Any clinically significant abnormalities will be recorded as AEs.

7.1.5 Clinical Safety Laboratory Tests

Blood and urine samples will be collected for standard clinical laboratory tests, including biochemistry, haematology, and urinalysis panels, as well as specific tests such as urine drug screening and alcohol tests (and urine/serum pregnancy tests for women of childbearing potential) at timepoints indicated in the Study Schedule of Events (see Attachment #1_Section 15.1).

The exact lists of parameters to be assessed are given in the Attachment #2_Section 15.2.

The results of laboratory tests performed during the screening phase must be obtained before dosing on Day 1.

7.1.5.1 Urinalysis

Freshly voided urine samples (at least 10 ml) will be collected to perform a dipstick assessment of the parameters described in Attachment #2_Section 15.2.

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

7.1.5.2 Pregnancy Test

A Beta-human chorionic gonadotrophin (ßHCG) serum test will be performed for all female subjects of childbearing potential at Screening (visit 1) and if clinically indicated thereafter. Human chorionic gonadotrophin (HCG) urine test will also be performed on Day-1 (baseline) and at the end-of-study visit. It may be repeated at any time during the study according to Investigator's judgement.

Any subject becoming pregnant during the study will be withdrawn. All pregnancies that occur during the study are to be reported as described in Section 7.1.1.8.

7.1.5.3 Investigator's Review

Investigators must document their review of each laboratory report by signing or initialling and dating each report. Laboratory values that fall outside a clinically accepted reference range or values that differ significantly from previous values will be evaluated.

When multiple laboratory values are out of range but not clinically significant, "all labs NCS" or a general comment may be written on the laboratory page. However, all clinically significant laboratory values must be individually marked with CS.

The Investigator will review the safety laboratory test results, document the review, and record any clinically relevant changes occurring or observed during the study in the AE section of the eCRF (see Section 7.1.1 for abnormal laboratory tests that should be recorded as AEs).

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

7.1.5.4 Sample Handling, Storage and Destruction

Full details related to the samples processing, labelling, storage, shipment and destruction procedures will be provided to the Investigator via separate instructions and archived in the Trial Master File (TMF).

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

7.1.6 Additional Definitions or Special Procedures

Not applicable.

7.2 Efficacy Assessment(s)

Not applicable.

7.3 Assessments of lead levels and other elemental impurities

The assessment of elemental impurities in blood and urine include lead and 8 other elemental impurities: i.e. arsenic, cadmium, mercury, cobalt, vanadium, nickel, barium and aluminium.

Other impurities may be assessed via Biobanking samples (See Attachment #5_Section 15.5).

7.3.1 Sampling Schedule

Urine collections (as 24-hour collection) and Blood samples for the measurement of elemental impurities will be collected as described in the Schedule of events (see Attachment #1_Section 15.1).

During the outpatient visits, blood samples will be collected pre-dose of any of the 3 dosing occasions of that day.

Taken into account the time window flexibility during the Day 35, the 24-hour urine collection should be done whilst subject is still under study treatment (e.g.: if subject performs the Day 35 at Day 36, Smecta® will be given until the evening of Day 36, or alternatively if subject comes at Day 34, the last Smecta® intake will be done at Day 34 evening).

7.3.2 Sampling Method for Pharmacokinetic Measurements

Blood samples (8 ml at each time point) will be collected as described in the Schedule of event (see Attachment #1_Section 15.1):

- For determination of lead in blood and 8 other elemental impurities in blood (arsenic, cadmium, mercury, cobalt, vanadium, nickel, barium and aluminium)
- Biobanking samples (blood): for potential assessment of other elemental impurities levels in blood
- Biobanking samples (serum): for potential assessment of lithium levels in serum

- Biobanking samples (plasma): for potential determination of lead in the plasma.

. During the study, the nominal sample collection times may be adjusted, but the total number of samples will not increase. The exact dates and times of blood sample collection, and Smecta® administration must be recorded in the eCRF.

Specific blood collection, preparation and storage conditions are described in a separate Study Laboratory Manual.

All urine samples collected over the specific 24-hour interval will be pooled and the total urine volume measured and recorded in the eCRF. From this pooled volume, 2 aliquots of 1.5 ml (primary, back-up) each will be obtained for the measurement of elemental impurities. Two additional urine aliquots of 1.5 ml (1 primary, 1 back-up) will be collected for the biobanking purpose.

Each tube should be labelled in accordance with the Sponsor's requirements. Aliquots will be shipped on dry ice.

Unless specified below, specific details of labelling, sampling, storing and shipping procedures will be described in separate documentation, and provided by the Sponsor.

7.3.3 Bio-analytical Method

Blood and urine samples will be analysed to determine concentrations of elemental impurities using a validated, specific and sensitive ICP-MS method by Quality Assistance (Donstiennes, Belgium). Assessment of lead and each elementary impurity in blood and urine will be performed under the supervision of Ipsen Pharmacokinetics and Drug Metabolism (PDM) Department.

7.3.4 Parameter Estimation

Individual blood concentrations for each elementary impurities will be listed and summarised by timepoint using descriptive statistics for continuous variables (number of available observations, mean, median, standard deviation (SD), minimum, maximum, geometric mean, and geometric coefficient of variation assuming log-normally distributed data).

PK parameters of lead may be calculated if feasible.

Change from baseline by timepoint will be assessed and summarised using descriptive statistics.

Individual urine concentrations for each elementary impurities will be listed and summarised by timepoint using descriptive statistics. Change from baseline by timepoint will be assessed and summarised using descriptive statistics

Descriptive summary statistics (the number of observations (n), mean, median, SD and range for continuous variables, and n and percentage (%) for categorical/nominal variables) will be presented.

7.4 Pharmacodynamic Assessment(s)

No pharmacodynamic assessment will be performed during this study.

7.5 Exploratory Assessment(s)

Single faces samples will be collected at timepoint defined in the schedule of events (see Attachment #1_Section 15.1) and processed according to standardised techniques developed by an international consortium (International Human Microbiome Standards, IHMS, http://www.microbiome-standards.org/#). Detailed procedures for the collection, handling, storage, shipment and analyses of the samples will be described in the specific study manual. The stools samples taken after the end of the treatment period (e.g. from Day 65 to Day 125 visits) will be analysed only in case of a significant change of microbiota is observed during

the study treatment in order to assess the resilience (return to the baseline profile) of microbiota during the post study treatment period.

Consistency of stools (recorded and rated according to Bristol scale) (See attachment # 7_ Section15.7) and frequency will be assessed over 24h by the subject the day before Screening, Day-14, baseline (D-1), Day 8, Day 35, Day 65, Day 95 and Day 125 visits, collected in a diary and reported by the site in the eCRF.

7.6 Compliance to Study Procedures

7.6.1 Compliance to Protocol

Every attempt will be made to select subjects who have the ability to understand and comply with instructions. Noncompliant subjects may be discontinued from the study. 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 Subject Diary). These will be recorded in the eCRF by the site. Drug accountability records will be maintained by the study site.

7.6.2 Compliance to Timing of Procedures

The specifications in this protocol for the timings and dates of primary tests are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor deviations within the allowed time windows specified in the Study Schedule of Events (see Section 15.1); however, the actual time must always be correctly recorded in the eCRF and other relevant source documents. Any excursion outside of these allowed time windows might be regarded as protocol violation.

Any major modification that might affect the conduct of the study, subject safety, and/or data integrity will be detailed in a protocol amendment.

8 STATISTICAL ANALYSES

8.1 Data Analysis Plan

8.1.1 General Considerations

Statistical analysis will be performed by a Sponsor selected CRO and according to ICH E9 guidelines and using SAS version 9.3 or higher (See references in Section 14).

8.1.2 Determination of 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% (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 enrol a total of 35 subjects to ensure that at least 29 subjects completed the study.

Subjects who prematurely discontinue after IMP administration will not be replaced.

8.1.3 Study Participant Disposition

The numbers and percentages of subjects enrolled and included in the safety population will be tabulated. The reasons for subject exclusions from the safety population will also be tabulated. In addition, the numbers of subjects who were treated, discontinued and completed will be tabulated.

Primary reasons for discontinuation of study treatment will be tabulated.

8.1.4 Study Participant Characteristics

Descriptive summary statistics (n, mean, SD, median, minimum, maximum) or frequency counts of demographic and baseline data (medical history, concomitant medications, etc.) will be presented for the safety population.

8.1.5 Statistical Evaluation of Safety

Safety analyses and summary tables will be based on the safety population. Adverse events reported by Investigators will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 19.0 or higher Version).

All safety data will be included in the subject data listings. Listings of AEs will be presented by subject, system organ class and preferred term.

All AEs and SAEs occurring during the Screening period will be reported; however, these will not be considered in the analysis of TEAEs.

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.

All TEAEs will be flagged in the AEs listings. The incidence of all reported TEAEs and SAEs will be tabulated. In addition, summary tables will be presented by maximum intensity, drug relationship and TEAEs associated with premature withdrawal of study medication.

Concomitant medication will be coded by using the World Health Organisation (WHO) Drug Dictionary (December 2015 Version or higher) with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

Summary statistics (mean, median, SD and range as appropriate) will be presented for vital signs (blood pressure and heart rate) and clinical laboratory tests on screening and end-of-study visit. For laboratory data, abnormal values will be flagged in the data listings and a list of clinically significant abnormal values will be presented. For the ECG parameters, clinically significant findings will be listed.

Further details of the statistical analyses will be available in a Statistical Analysis Plan developed the CRO per Sponsor agreement and approval.

8.1.6 Analyses and Statistical Inference

Individual listings and summary tables of Elemental Impurities concentrations in blood and in urine will be provided.

8.2 Preliminary and/or 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 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.

9 DATA HANDLING AND RECORD KEEPING

9.1 Data Capture

The following source data may be generated and handled for further data basing process:

- Paper-based or electronic data captured in Case Report Forms
- Paper-based or electronic data captured systems, other than the case Report Forms
- Paper or electronic data from local or external vendors.

To ensure accurate, complete, and reliable data, the Sponsor or its representative will provide instructional material to the study site(s), as appropriate. Training session will be given during a start-up/initiation meeting for instructions on the completion/data entry of any source data documents and electronic Case Report Forms.

The Investigators or their designees must verify that all data entries in the eCRFs are accurate and correct. If certain information is not available for a particular timepoint and/or subject, specific instructions should be followed, e.g. to document that the procedure was either not done (ND) or not applicable (NA).

Every effort should be made to ensure that all safety evaluations are completed by the same individual who made the initial baseline determination.

9.2 Data Handling

All or part of the data will be monitored at periodic visit to the study site, according to a monitoring plan. All entries in the eCRFs, corrections and alterations are to be made by the responsible Investigator or his/her designee.

Once monitored and cleaned, the paper-based data (either source or transcribed data) that have been selected for populating the database will follow a single entry process. Electronic data will be directly entered in the database.

Details of all data management procedures, from the initial planning to the archiving of final datasets/documents following database freeze/lock will be documented in appropriate data management and validation plan(s). Among others, these procedures will also describe quality control checks, data handling process for any missing, unused or spurious data, as well as coding procedures for AE's, medical history, physical examination and medications.

9.3 Record Keeping

The Investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes.

Depending on the data collected and the type(s) of data, records will be kept following storage, and archiving procedures agreed by the Sponsor/Investigator site involved in this study, and in accordance to any regulations that are applicable in the country(ies) where the study is conducted.

10 REGULATORY AND ETHICAL CONSIDERATIONS

The study will be conducted in compliance with independent ethics committees/institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Any episode of noncompliance will be documented. The Electronic Data Capture (EDC) system will comply with the Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerised Systems Used in Clinical Trials.

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

10.1 Subject Information Sheet and Consent

The Investigator is responsible for ensuring that the subject understands the potential risks and benefits of participating in the study, including answering, orally and/or in writing, to any questions the subject may have throughout the study and sharing any new information that may be relevant to the subject's willingness to continue his or her participation in the study in a timely manner.

The subject information sheet and consent document will be used to explain the potential risks and benefits of study participation to the subject in simple terms before the subject is entered into the study, and to document that the subject is satisfied with his or her understanding of the study and desires to participate.

The Investigator is ultimately responsible for ensuring that the Ethics Committee (EC) approved informed consent is appropriately signed and dated by each subject prior to the performance of any study procedures. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations.

10.2 Ethical Review Considerations

The following documents should be submitted to the relevant ECs for review and approval to conduct the study (this list may not be exhaustive):

- Protocol/amendment(s) approved by the Sponsor,
- Currently applicable SmPC or package labelling,
- Relevant Investigator's curriculum vitae,
- Subject information and informed consent document(s) and form(s),
- Subject emergency study contact cards
- Recruitment procedures/materials (advertisements), if any.

The EC(s) will review all submission documents as required, and a written favourable opinion for the conduct of the study should be made available to the Investigator before initiating the study. This document must be dated and clearly identify the version number(s) and date(s) of the documents submitted/reviewed and should include a statement from the EC that they comply with GCP requirements.

The study may begin at the investigative site(s) only after receiving this dated and signed documentation of the EC approval or favourable opinion.

During the study, any update to the following documents will be sent to the EC either for information, or for review and approval, depending on how substantial the modifications are: (1) SmPC; (2) reports of SAEs; (3) all protocol amendments and revised informed consent(s), if any.

At the end of the study, the Ethics Committee will be notified about the study completion.

10.3 Regulatory Considerations

This study will be conducted in accordance with applicable laws and regulations, GCPs, and the ethical principles that have their origin in the Declaration of Helsinki.

All or some of the obligations of the Sponsor will be assigned to a Clinical Research Organisation (CRO).

An identification code assigned to each subject will be used in lieu of the subject's name to protect the subject's identity when reporting AEs and/or other trial-related data.

10.4 Final Report Signature

The Investigator or designee will proposed to review and sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusion of the report.

11 INSURANCE AND FINANCE

11.1 Insurance

The Sponsor declares that it has taken out a product liability insurance covering all subjects screened and enrolled in this study in respect to risks involved in the study.

11.2 Financial Agreement

Since this study is to be performed in partnership with a CRO, separate financial agreements between the Sponsor and the CRO on one side, and the CRU and the CRO on the other side, will be signed prior to initiating the study, outlining overall Sponsor and Investigators responsibilities in relation to the study.

12 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will provide instructional material to the study sites, as appropriate. A start-up training session will be done prior to screening start to instruct the Investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and all study procedures.

12.1 Protocol Amendments and Protocol Deviations and Violations

12.1.1 Protocol Amendments

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

12.1.2 Protocol Deviations, Violations, and Exceptions

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

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

As a matter of policy, the Sponsor will not grant exceptions to protocol-specific entry criteria to allow subjects to enter a study. If under extraordinary circumstances such action is considered ethically, medically, and scientifically justified for a particular subject, prior approval from the Sponsor and the responsible IRB/IEC is required before the subject will be allowed to enter the study.

If investigative clinical unit personnel learn that a subject who did not meet protocol eligibility criteria was entered in a study (protocol violation), they must immediately inform the Sponsor. Such subjects will be discontinued from the study, except in an exceptional instance, following review and written approval by the Sponsor and the responsible IRB/IEC.

12.1.3 Information to Study Personnel

The Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting any study procedures and during the course of the study (e.g. when new staff become involved).

The Investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the clinical unit authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

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

12.2 Monitoring

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

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

Before the study initiation visit, the Sponsor assigned study monitor will write a monitoring plan indicating the monitoring procedures and at which occasions during the study monitoring visits will be performed.

Periodic visits will be made to the study site throughout the study at mutually agreeable times. Any appropriate communication tools will be set up to ensure the Sponsor and/or its representative is/are available for consultation, so they can stay in contact with the study site personnel.

Adequate time and space for monitoring visits should be made available by the Investigator.

The Investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas) for the purpose of verifying entries made in the eCRF, and assist with the monitor's activities, if requested.

Quality of the paper-based or electronic data will be reviewed to detect errors in data collection and, if necessary, to verify the quality of the data.

The eCRF is expected to be completed an ongoing basis to allow regular review by the study monitor, both remotely by the internet and during site visits. The study monitor will use functions of the electronic data capture (EDC) system to address any queries raised while reviewing the data entered by the study site personnel in a timely manner.

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

12.3 Investigator's Regulatory Obligations

All clinical work under this protocol will be conducted according to GCP rules. This includes that the study may be audited at any time by a Quality Assurance personnel designated by the Sponsor, or by regulatory bodies. The Investigator must adhere to the GCP principles in addition to any applicable local regulations.

If requested, the Investigator will provide the Sponsor, applicable regulatory agencies, and applicable Ethics Committee with direct access to any original source documents.

The Investigator(s) should demonstrate due diligence in recruitment and screening of potential study subjects. The enrolment rate should be sufficient to complete the study as agreed with the Sponsor. The Sponsor should be notified of any projected delays, which may impact the completion of the study.

12.3.1 Audit and Inspection

Authorised personnel from external CAs and the Sponsor's authorised quality assurance personnel may carry out inspections and audits.

12.3.2 Data Quality Assurance

Monitored eCRF, transferred from the clinical unit to the assigned data management group, will be reviewed (secondary monitoring) for completeness, consistency, and protocol compliance.

Reasons should be given in the relevant eCRF for any missing data and other protocol deviations. Any electronic queries and items not adequately explained will require additional electronic manual queries to be raised to the Investigator for clarification/correction. The

Investigator must ensure that queries are dealt with promptly. All data changes and clarifications can be viewed in the audit trail function of the eCRF.

13 PUBLICATION POLICY

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

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

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

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

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15 ATTACHMENTS

15.1 Attachment 1 – Study Schedule

Study Schedule of Events - Protocol D-FR-00250-108

	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).

15.2 Attachment 2 – Safety Clinical Laboratory Tests

	Scre/ Bas	EoS/ ED		Scre/ Bas	EoS/ ED
Haematology			**Clinical Chemistry**		
Haematocrit	x	x	Sodium	x	x
Haemoglobin	x	x	Potassium	x	x
Erythrocyte count (RBC)	x	x	Bicarbonate	x	x
Mean cell volume (MCV)	x	x	Chloride	x	x
Mean cell haemoglobin (MCH)	x	x	Calcium	x	x
Mean cell haemoglobin concentration (MCHC)	x	x	Phosphorus	x	x
Leukocytes (WBC)	x	x	Iron	x	x
Absolute counts of:			Transferrine saturation	x	x
Neutrophils	x	x	Ferritin	x	x
Lymphocytes	x	x	Glucose (fasting)[a]	x	x
Monocytes	x	x	Amylase	x	x
Eosinophils	x	x	Lipase	x	x
Basophils	x	x	Urea	x	x
Platelets	x	x	Total cholesterol	x	x
			Total protein	x	x
Coagulation			Albumin	x	x
Activated partial thromboplastin time	x	x	Total bilirubin	x	x
Prothrombin time and derived measures of prothrombin ratio	x	x	Conjugated bilirubin	x	x
INR	x	x	Alkaline phosphatase (ALP)	x	x
			Aspartate aminotransferase (AST)	x	x
			Alanine aminotransferase (ALT)	x	x
			Creatinine	x	x
			Gamma-glutamyl transferase (GGT)	x	x
			Triglycerides (TG)	x	x
			eGFR [c]	x	x
			Glycated Haemoglobin (A1C)	x	x
Urinalysis [f]			Uric acid	x	x
pH	x	x	C-reactive protein (CRP)	x[g]	
Protein	x	x	**Specific Tests**		
Glucose	x	x	Ethanol testing [d]	x	
Ketones	x	x	Urine drug screen [d], including at least amphetamines, methamphetamines, benzodiazepines, cocaine, opiates, THC and barbiturates	x	
Bilirubin	x	x			
Urobilinogen	x	x			
Blood	x	x	Serum Pregnancy test (women of child bearing potential) [e]	x	
Nitrite	x	x	Hepatitis B surface antigen	x	
Microscopic examination of sediment (if indicated) [b]	Opt.	Opt.	Hepatitis C	x	
Pregnancy test [e]	x	x	HIV	x	

Scre = Screening visit(s), Bas = Baseline, EoS = End of Study, ED = Early Discontinuation, Opt. = Optional

a Glucose measured in fasting conditions

b will not be collected in the eCRF unless clinically significant

c calculated by CKD-EPI or MDRD formula or equivalent (NKDEP 2014)

d Ethanol and urine drug testing to be performed at least once at the admission to the CRU before dosing

e Serum pregnancy test at screening only, on urine at baseline and discharge from the study (EoS/ED)

f Urinalysis performed via dipstick.

g C-reactive protein (CRP) only at Screening visit

15.3 Attachment 3 – Blood Sampling Summary

This table summarises the maximum number of (veni) punctures and blood volumes for all blood sampling (screening, safety laboratories and bio-analytical assays) during the study.

Fewer venipunctures and blood draws may actually occur if needed for safety purposes, but this will not require a protocol amendment.

Purpose	**Maximum Blood volume per sample (ml)**	**Maximum Number of Blood Samples**	**Maximum Total Volume (ml)**
Screening			
Clinical laboratory tests: Haematology and Biochemistry, Coagulation, HbA1C, Serology, Endocrine, Serum pregnancy test	25	1	25
Provision for repeat tests (local laboratory)	20	1	20
Study			
Elemental Impurities assays	2	23	46
Biobanking for Elemental Impurities	2	23	46
Biobanking for Plasma lead assay	4	23	92
Catheter flushes, if any	2	12	24
Clinical laboratory tests: Haematology and Biochemistry, coagulation	13.5	2	27
Provision for unscheduled additional sampling	50	1	50
Total over 5,5 months		**Approximately 330ml**	

15.4 Attachment 4 – List of Excluded Previous and Concomitant Medications

Exclusion related to study drug: diosmectite (Smecta®).

Drugs with narrow therapeutic index and requiring daily administrations: e.g.

Aminophylline, Carbamazepine, Clindamycin, Clonidine, Digoxin, Disopyramide Dyphylline, Guanethidine, Isoetharine, Isoproterenol, Levoxyine, Lithium, Metaporterenol, Minoxidil, Oxytriphylline, Phenytoin, Prazosin, Primidone, Procainamide, Quinidine, Theophylline, Valproate… (non exhaustive list).

Exclusion related to primary end point:

Any products of mineral origin:

- Diosmectite (except as prescribed in the present study as Smecta®) and similar
- Other clay compounds or mineral extracts (used as medicinal products, medical devices or even potentially as food supplement).
  - Clays: Examples included (not limited): Attapulgite (e.g. Actapulgite®, Gastropulgite®), montmorillonite beidellitique (e.g. Bedelix®, Gelox®), but also Kaolin, Talc
- Activated charcoal.

Compounds containing a significant amount of Aluminium Hydroxyde and/or Magnesium Hydroxide such as Maalox®, Xolaam®, Rocgel®, Moxydar®, Gelox®, Phosphalugel®, Polysilane®, …

Exclusion related to ancillary study (digestive microbiota):

- Any Antibiotic agents
- Metformin
- PPI (Proton Pump Inhibitor)

15.5 Attachment 5 – List of Classes I - III Elemental Impurities (ICH Q3D), Additional Elements and Strategy for Analyses (Primary (I), Secondary (II), or Biobanking)

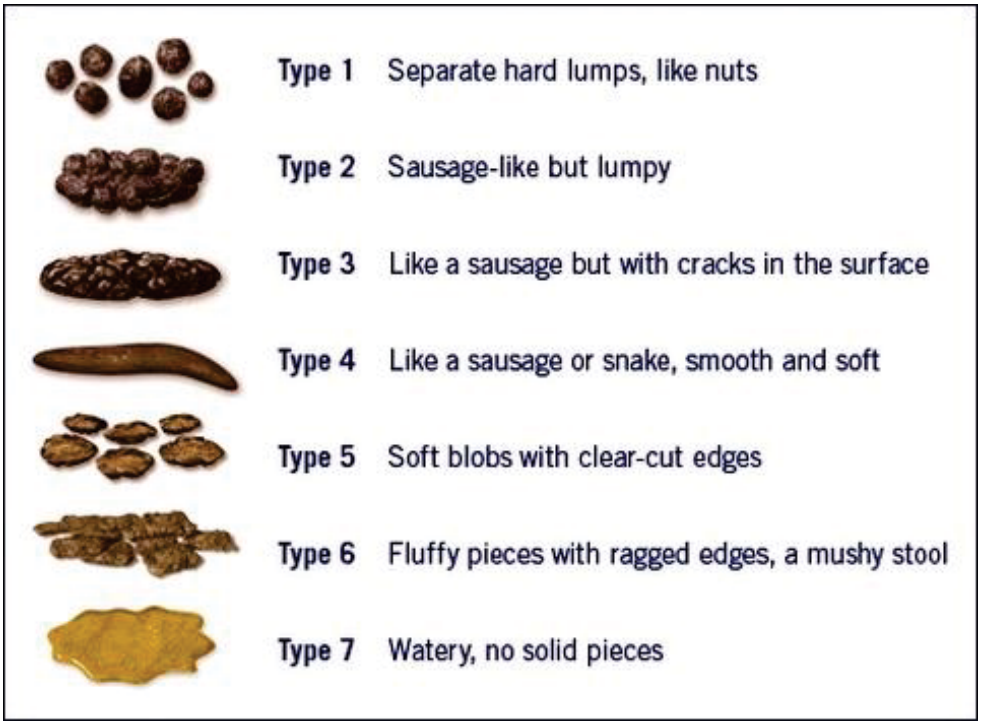
Element	Class (Q3D)	Primary/Secondary/Biobanking
Cd	1	Secondary
Pb	1	Primary
As	1	Secondary
Hg	1	Secondary
Co	2A	Secondary
V	2A	Secondary
Ni	2A	Secondary
Tl	2B	-
Au	2B	-
Pd	2B	-
Ir	2B	-
Os	2B	-
Rh	2B	-
Ru	2B	-
Se	2B	-
Ag	2B	-
Pt	2B	-
Li	3	Biobanking
Sb	3	Biobanking
Ba	3	Secondary
Mo	3	Biobanking
Cu	3	Biobanking
Sn	3	Biobanking
Cr	3	Biobanking
Al	Not Listed	Secondary
Mn	Not Listed	Biobanking
Zn	Not Listed	Biobanking
B	Not Listed	Biobanking
Ca	Not Listed	Biobanking
Fe	Not Listed	Biobanking
K	Not Listed	Biobanking
Mg	Not Listed	Biobanking
Na	Not Listed	Biobanking
W	Not Listed	Biobanking

15.6 Attachment 6 – List of Jobs or Activities bearing risk of lead exposure (INRS website, health and safety at work)

MAIN ACTIVITIES AREAS EXPOSED TO LEAD	
Building	• Work with paints and pipes in old buildings (e.g. removal, repair…), • Cutting or sanding of metallic structures covered with anticorrosive paint • roof works (e.g. welding with lead, the use of lead sheets …)
Manufactory	• Manufacturing and recycling of batteries, • Manufacturing of ceramics (e.g. tiles…), • Metal industry, in particular the foundries of brass alloys, • Recycling of electronic products, • Manufacturing of paints, • Plastics processing industry, • Manufacturing of special glasses and crystal, • repair of radiators of machines and heavy trucks
Handicraft	• Manufacturing and repair of stained-glass windows, • Pottery, • Artistic foundry • Jewellery
Other	• firing range

http://www.inrs.fr/risques/plomb/ce-qu-il-faut-retenir.html#f0e92310-6003-4e09-8184-579e026f02b9

15.7 Attachment 7 – Bristol Stool Form Scale



Lewis, SJ and KW Heaton, 1997, Stool Form Scale as a Useful Guide to Intestinal Transit Time, Scand. J. Gastroenterol, 32(9):920-4.

15.8 Attachment 8 – Protocol Amendment Summary

All additions have been identified by the use of underline and all deletions by ~~strikethroughs~~.

Front page

Pharmacovigilance contact details:

PPD Global Patient Safety, Ipsen Biopharm Ltd

~~190 Bath Road, Slough, Berkshire SL1 3XE, England~~ 102 Park Drive, Milton Park, Oxfordshire, OX14 4RY, England

Tel: PPD

Mob: PPD

~~For serious adverse events (SAEs) reporting:~~

~~Fax:~~ PPD

3.3.1.4 Post-Treatment Period

The subjects will be asked to come back to the CRU at two occasions during the post-treatment period: these visits should occur at Week 9 (Visit 8) and at Week 13 (Visit 9). At Visit 8 and 9, blood sampling will be collected as well as 24-hour urine collection for impurities dosing. Stools samples will be collected only at Visit 8 (week 9) and Visit 9 (Week 13).

7.3.2.Sampling Method for Pharmacokinetic Measurements

~~Blood samples (2 ml each) for determination of elemental impurities concentrations measurement in blood will be collected as described in the Schedule of event (see Attachment #1_Section 15.1). Additional blood samples (2 ml each) will be biobanked at the timepoints described in the Schedule of event (see Attachment #1_Section 15.1), in order to further assay other elemental impurities levels in blood. Additional blood samples (4 mL each) will be taken and prepared; the resulting plasma samples will be biobanked for potential determination of lead in the plasma.~~

Blood samples (8 ml at each time point) will be collected as described in the Schedule of event (see Attachment #1_Section 15.1):

- For determination of lead in blood and 8 other elemental impurities in blood (arsenic, cadmium, mercury, cobalt, vanadium, nickel, barium and aluminium)
- Biobanking samples (blood): for potential assessment of other elemental impurities levels in blood
- Biobanking samples (serum): for potential assessment of lithium levels in serum
- Biobanking samples (plasma): for potential determination of lead in the plasma

During the study, the nominal sample collection times may be adjusted, but the total number of samples will not increase. The exact dates and times of blood sample collection, and Smecta® administration must be recorded in the eCRF.

Specific blood collection, preparation and storage conditions are described in a separate Study Laboratory Manual.

All urine samples collected over the specific 24-hour interval will be pooled and the total urine volume measured and recorded in the eCRF. From this pooled volume, 2 aliquots of ~~2~~ 1.5 ml (primary, back-up) each will be obtained for the measurement of elemental impurities

~~as well as for the biobanking purpose~~. Two additional urine aliquots of 1.5 ml (1 primary, 1 back-up) will be collected for the biobanking purpose.

Each tube should be labelled in accordance with the Sponsor's requirements. Aliquots will be shipped on dry ice.

Unless specified below, specific details of labelling, sampling, storing and shipping procedures will be described in separate documentation, and provided by the Sponsor.

7.5. Exploratory Assessment(s)

Single faces samples will be collected at timepoint defined in the schedule of events (see Attachment #1_Section 15.1) and processed according to standardised techniques developed by an international consortium (International Human Microbiome Standards, IHMS, http://www.microbiome-standards.org/#). Detailed procedures for the collection, handling, storage, shipment and analyses of the samples will be described in the specific study manual. The stools samples taken after the end of the treatment period (e.g. from Day 65 to Day 125 visits) will be analysed only in case of a significant change of microbiota is observed during the study treatment in order to assess the resilience (return to the baseline profile) of microbiota during the post study treatment period.

Consistency of stools (recorded and rated according to Bristol scale) (See attachment # 7_ Section15.7) and frequency will be assessed over 24h by the subject the day before ~~at~~ Screening, Day-14, baseline (D-1), ~~the day before Visit~~ Day 8, ~~at~~ Day 35, Day 65, ~~and~~ Day 95 and Day 125 visits, collected in a diary and reported by the site in the eCRF.

Study Schedule of Events - Protocol D-FR-00250-108

	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)

15.3 Attachment 3 – Blood Sampling Summary

This table summarises the maximum number of (veni) punctures and blood volumes for all blood sampling (screening, safety laboratories and bio-analytical assays) during the study.

Fewer venipunctures and blood draws may actually occur if needed for safety purposes, but this will not require a protocol amendment.

Purpose	**Maximum Blood volume per sample (ml)**	**Maximum Number of Blood Samples**	**Maximum Total Volume (ml)**
Screening			
Clinical laboratory tests: Haematology and Biochemistry, Coagulation, HbA1C, Serology, Endocrine, Serum pregnancy test	25	1	25
Provision for repeat tests (local laboratory)	20	1	20
Study			
Elemental Impurities assays	2	23	46
Biobanking for Elemental Impurities	2	23	46
Biobanking for Plasma lead assay	4	23	92
Catheter flushes, if any	2	12	24
Clinical laboratory tests: Haematology and Biochemistry, coagulation	13.5	2	27
Provision for unscheduled additional sampling	50	1	50
Total over 5,5 months		**Approximately 330ml**	