DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL

A Phase 1, Blinded, Randomized, Placebo-Controlled, Parallel-Group, Single-Dose, Dose-Escalation Study to Investigate Safety, Tolerability, and Pharmacokinetics of Emodepside (BAY 44-4400) After Oral Dosing in Healthy Male Subjects

Short title	Emodepside Single Dose-Escalation in Healthy Male Subjects
Name of product(s)	Emodepside (BAY 44-4400)
Drug Class	Anthelmintic cyclooctadepsipeptide
Phase	1, First-in-Human study (FiH)
Indication	Treatment of onchocerciasis (river blindness)
Clinical Trial Protocol Number	DNDI-EMO-001
EudraCT	2015-003592-29
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Principal Investigator	Dr. Malcolm Boyce
Clinical Trial Protocol Version / Date	Version 5.0, Final / Date: 18 January 2017
Protocol Amendment Number / Date	Not Applicable

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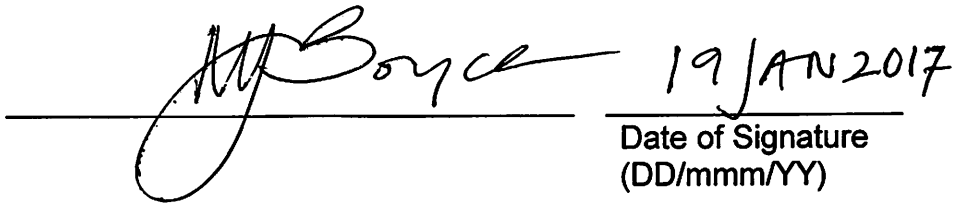
Investigators Signature Page

I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this trial. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the trial.
I will use only the informed consent form approved by the sponsor or its representative and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) responsible for this trial if required by national law.
I agree that the sponsor or its representatives shall have access to any source documents from which case report form information may have been generated.

Principal Investigator at trial site

Investigator Signature	 19 JAN 2017 Date of Signature (DD/mmm/YY)
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ABBREVIATIONS – GLOSSARY OF TERMS

ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
bw	Body weight
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CL	Clearance (total)
Cmax	Maximum concentration
Cmin	Minimum concentration
CNS	Central nervous system
CRF	Case report form
CTA	Clinical Trial Application
CV	Coefficient of variation
DALY	Disability Adjusted Life Years
DNDi	Drugs for neglected diseases initiative
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
FDA	Food and Drug Administration
F_{rel}	The average relative bioavailability
ICF	Informed Consent Form
IEC	Independent ethics committee
FIH	First in Human
FIM	First in Man
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HbA1C	Glycated haemoglobin
HDL	High density lipoprotein
HED	Human equivalent dose
HIV	Human immunodeficiency virus
HMR	Hammersmith Medicines Research Ltd
HR	Heart rate
ICH	International Conferences on Harmonisation

IMP	Investigational Medicinal Product
IR	Immediate Release
IV	Intravenous
LDH	Lactate dehydrogemnase
LDL	Low density lipoprotein
LF	Lymphatic Filariasis
LIMS	Laboratory Information Management System
LSF	Liquid Service Formulation
MCH	Hemoglobin amount per red blood cell
MCHC	The amount of hemoglobin relative to the size of the cell (hemoglobin concentration) per red blood cell
MCV	Average red blood cell size
MDA	Massive Drug Administration
MedRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimum Inhibitory Concentration
MRT	Mean residence time
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NRES	National Research Ethics Service
OCP	Onchocerciasis Control Programme
PI	Principal investigator
PK	Pharmacokinetics
PT	Prothrombin Time
QA	Quality Assurance
QTcB	QTc Bazett’s formula
QTcF	QTc Fridericia's formula
RBC	Red blood cell
REC	Research Ethics Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SRG	Safety Review Group
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TK	Toxicokinetic
Tmax	Maximum Time
TSH	thyroid stimulating hormone
ULN	Upper limit of normal
UV	Ultraviolet
Vs	Volume
WBC	White blood cell
WHO	World Health Organization

PROTOCOL SUMMARY

Background Information	**Background Information** Filarial diseases cover infectious diseases caused by parasitic nematode worms onchocerciasis (river blindness), lymphatic filariasis (LF, or elephantiasis), and loiasis (African eye worm, or *Loa loa*). More than 1 billion of the world's poorest people are at risk.[24,25] An estimated 120 million people suffer from LF, and about 80% of people at risk live in the following 10 countries: Bangladesh, Democratic Republic of Congo, Ethiopia, India, Indonesia, Myanmar, Nigeria, Nepal, Philippines, and the Republic of Tanzania.[25] Loiasis occurs exclusively in West and Central Africa, an estimated 13 million are infected with *Loa loa*.[12] An estimated 37 million[20] suffer from onchocerciasis, with 99% cases in 31 African countries, and 169 million at risk. Although the disease is almost exclusively confined to West and Central Africa, some foci exist in Yemen and South America (Brazil and Venezuela). [12,23] The burden associated to onchocerciasis is estimated at nearly 600'000 disability-adjusted life years (DALYs) worldwide.[22] Severe visual impairment and blindness are considered the most severe complication of the disease and their control was the main objective of the initial control program: the Onchocerciasis Control Programme (OCP) in West Africa. However skin lesion and itching represent a significant public health problem in affected communities. Incessant itching may cause insomnia, affects work productivity and social relationships and can even induce a premature child weaning by affected mothers.[1] Onchocerciasis is still the world's second-leading infectious cause of blindness. The World Health Organization (WHO) estimates that 746'000 patients are visually impaired, 265'000 are blinded and more than 4 million suffer from severe itching.[22] *Onchocerca* is a helminth of the genus nematode (roundworm), causing onchocerciasis in humans. The disease is contracted through the bite of an infected vector, a female blackfly of the genus *Simulium*, which transmits infective larvae (L3) to a person. Once injected in the host, the larvae molt twice before reaching adult stage. An adult worm can then live for 15 years in the human body.[9] Adult worms settle into fibrous nodules in the human body close to the surface of the skin or near the joints. Adult males migrate from nodule to nodule. After mating, a female releases about 1,000 new microfilariae larvae per day. The microfilariae migrate through the skin where they are eventually ingested by a blackfly in which the parasite completes its life cycle by molting twice into an infective larvae. These larvae may then be transferred to another host to continue the cycle.
Rationale for the Development of Emodepside	The programs for the treatment and control of filarial diseases through Mass Drug Administration (MDA) have been in place for over 20 years with an important success in reducing transmission and morbidity. However, current treatments must be repeated at regular intervals for the life of the adult worm (up to 15 years), making implementation extremely difficult in endemic countries. Additionally, the programs have to be implemented with special measures in regions of *Onchocerca* infection where patients are co-infected with *Loa loa*.[16] This limits the use of ivermectin in MDA programs in co-endemic areas, and

	is an impediment to achieving WHO elimination goals for onchocerciasis. Furthermore, reports of a suboptimal parasite response to ivermectin may be a sign of developing resistance.[16] Thus, there is an urgent need for a macrofilaricide, targeting onchocerciasis worms for use in individual case management and, after appropriate testing, as an alternative treatment in MDA programs. A macrofilaricidal drug could reduce the number of MDA cycles needed, thereby easing program implementation and enhancing chances in disease elimination, particularly in *Loa loa* co-endemic areas. Emodepside (BAY 44-4400) Emodepside is a registered drug for animal health, commercialized by Bayer Health Care under the name of Profender® (in combination with praziquantel) or Procox® (in combination with toltrazuril). Emodepside is a cyclooctadepsipeptide anthelmintic drug stimulating presynaptic receptors belonging to the secretin receptor family, resulting in flaccid paralysis of parasitic nematodes. Emodepside also interacts with SLO−1, a calcium activated potassium channel. Emodepside is being investigated for the oral treatment of onchocerchiasis caused by nematode parasites ("river blindness"). The advantage of emodepside over ivermectin, is to target different life stages of the parasites including the adults at lower concentrations. Targeting the adult form of the worm parasite should result in the reduction of the number of treatment cycles required to free the patient of infection and hopefully in allowing for treatment in regions *Loa loa* co infection is present. Hence, emodepside can be considered as a promising drug candidate able to fulfill unmet medical needs for the treatment of onchocerciasis.
Study Objectives	**Primary Objective:** • To investigate the safety and tolerability of emodepside (BAY 44-4400) after single oral doses administered as solution or immediate release (IR) tablets in healthy male subjects. **Secondary Objectives:** • To investigate the pharmacokinetics (PK) of emodepside (BAY 44-4400), after administration as oral solution, and IR tablet (optional). • To conduct an exploratory investigation of the relative bioavailability of the 5 mg and 20 mg IR tablet formulation using data generated in this study (optional). • Possibility to determine the effect of food on the bioavailability of emodepside (BAY 44-4400) after single oral doses administered as solution or IR tablets.
Study Endpoints	**Safety and Tolerability Variables:** • Adverse Events (AEs). • Physical and Neurological examination findings (including assessments of alertness, speech, language, and comprehension; cranial nerves; motor exam; coordination/cerebellar function; tremor of the hands, legs and head (postural, kinetic and rest tremor); sensation; and gait and postural stability (Pull test); mood; and

	sleepiness.) • Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP) in supine and sitting position (Part 2, Cohort 10 only in supine position), weight, body mass index (BMI; height at screening only), oral temperature. • 12-lead ECG (HR, PR, QRS, QTcF); and for selected cohorts 12-lead ECG continuous recording (for emodepside exposure response analysis - heart rate, PR, QRS and QTcF) • Clinical laboratory parameters: Hematology: hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocytes, white blood cells (WBC) including differential, red blood cells (RBC), glycated haemoglobin (HbA1C) (at screening); Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT); Biochemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), amylase, lipase, free T3 and T4, thyroid-stimulating hormone (TSH), glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride, and magnesium in serum; Urinalysis: by dipstick - glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites; • Ophthalmology assessments (Part 2, Cohort 10) **Pharmacodynamic Variables:** • Profiles of glucose and insulin (Parts 1 and 2, all cohorts), and glucagon and cortisol (Part 1, and Part 2, Cohort 9 only), only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1. • Single samples of prolactin and leptin, only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1 (Part 1 and Part 2, Cohort 9 only). **PK Variables:** Based on the plasma concentration time data (collected after administration of oral solution, or IR tablet), the following PK parameters will be calculated, and compared between the 2 different administrative forms of emodepside. • Main PK parameters: AUC_{∞}, AUC_{∞}/D, C_{max}, C_{max}/D, of emodepside (BAY 44-4400) • Exploratory PK parameters: $C_{max,norm}$, T_{max}, $t_{½}$, MRT, CL/F, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$, V_z/F of emodepside (BAY 44-4400) • Other parameters: λ_z, $AUC_{t-\infty}$, points terminal Optionally, the relative bioavailability of the IR tablet will be calculated: F_{rel} The following PK parameters of metabolites may be calculated: AUC_{∞}, AUC_{∞}/D, C_{max}, C_{max}/D, $C_{max,norm}$, T_{max}, $t_{½}$, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$. In urine, the amount and concentration of emodepside and possibly its metabolites will be measured. The appropriate specific PK parameters to be calculated will be decided according to the concentration.
Study Design	This will be a single-center, blinded, randomized, placebo-controlled,

	parallel–group, single-dose, dose-escalation, comparison study investigating safety, tolerability, and PK of emodepside, after administration as fasted or fed doses of oral liquid service formulation (LSF) or immediate release (IR) tablets in healthy male subjects. Optionally, a single dose of a 5 and 20 mg IR tablet formulation will be tested subsequently to the completion of the respective dose steps of the single-dose escalation with oral solution. Because emodepside has never been given to humans before, the first dose will be staggered. Two leading subjects will be dosed no later than the day before the remaining subjects in Cohort 1 will be dosed. To maintain the blind nature of the study, it will be ensured that 1 of the leading subjects, and 1 of the remaining subjects, are randomized to receive placebo. The study will be performed in a single site specialized in Phase 1 studies. For each subject the study starts with the Screening Visit, which can be up to 4 weeks before the profile day (dosing). Subjects who participate in Cohort 10, will attend a second Screening visit for ophthalmology assessments, if all other screening assessments show that they're suitable. For eligible subjects, admission to the ward will be at latest the evening before the Pre-Day. One dose step per subject consists of one Pre-Day, one Profile Day and an in-house observation period of 7 days after administration of test substance. Subjects will be discharged from the study ward 7 days after administration of test substance provided there are no medical objections (Day 7) (Follow-Up Option 1). However, if it is observed that mean half-life of emodepside in any previous cohort is longer than expected from the preclinical PK of 36 hours, and plasma concentrations of emodepside are still present 7 days after dosing, 2 alternative options may be employed to follow subjects after Day 7 (Figure 2) from Cohort 5 onwards and for all subjects in subsequent cohorts (this decision will be made during the Safety Review Meetings): • Option 2: addition of up to 4 out-patient follow-up visits with measurements for safety and blood samples for PK over a period up to an additional 14 days (ie, up to Day 21); or • Option 3: prolongation of the in-house period of up to an additional 7 days (ie, up to Day 14) with additional measurements for safety and blood samples for PK on up to 4 days during that period In all cases, approximately three weeks after their dose of study medicine (Day 21) the subjects will undergo their final examinations in a Follow-Up Visit. In Part 2, Cohorts 9 and 10 will follow Option 2. The out-patient visits for Cohort 9 will be decided at the dose decision meeting for that cohort. Cohort 10 will have out–patient visits on Days 10, 14 and 18.
Rationale for Study Design	This study applies a standard Phase I single dose escalation design. The data from this Single Ascending Dose study will be used to design subsequent Phase I studies of emodepside (eg, additional food effect and multiple ascending dose studies). The study is performed in a blinded design, in which the subjects and the study personnel (investigators and nurses) are blinded. The decision about dose escalation will be taken in the Safety Review Meeting prior to each new dose step (see 'Safety Review' section.) The rationale for the starting dose, and selection of study population are

	covered in the section ”Rationale of study design and dosing”. The rationale for the 7 day in-house period is based on an assumed dominant half-life of emodepside of 36 hours, derived from pharmacokinetics in dog and rat after oral administration. Applying the convention of in-house stay corresponding to 5 half-lives: 36h x 5 = 180h, equivalent to 7.5 days. However this may be extended if subjects have relevant plasma concentrations in early dose steps.
Main Entry Criteria	**Inclusion:** • Male, Caucasian volunteers, deemed healthy on the basis of a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine. Optionally, after further evaluation during the study, at the sponsor’s discretion other ethnic groups may be recruited. • 18 to 55 years of age • Normal body weight (BMI; Quetelet index) in the range of 18 and 30.1 kg/m^2 at screening • Sufficient intelligence to understand the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial. • Willingness to give written consent to participate, after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or his delegate • Willingness to give written consent to have data entered into The Overvolunteering Prevention System **Exclusion:** • Participation in another clinical trial within 3 months prior and during the study, or 5-times the half-life of the drug tested in the previous clinical trial, whichever is longer. (time calculated relative to the last dose in the previous clinical trial) • Clinically relevant abnormal medical history, concurrent medical condition, acute or chronic illness or history of chronic illness sufficient to invalidate the subject's participation in the trial or make it unnecessarily hazardous • Surgery (eg stomach bypass) or medical condition that might affect absorption of study drug taken orally • Presence of abnormal physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the subject • Blood pressure and heart rate in supine position at the screening examination outside one (or more) of the ranges 90–140 mm Hg systolic, 60–90 mm Hg diastolic; heart rate 40-100 beats/min. Subject with vital signs outside the reference range for the population being studied may be included, at the investigator’s discretion, if it is unlikely to introduce additional risk factors and will not interfere with study procedures

	• Loss of more than 400 mL of blood within the previous 3 months • History of relevant diseases of vital organs, of the central nervous system or other organs • Subjects with a medical or psychiatric disorder, condition or history of such that would increase the risk associated with study participation, or impair the subject's ability to participate or complete this study, in the opinion of the investigator or the sponsor • Positive tests for hepatitis B & C, HIV • Febrile illness within 1 week before the start of the study • Subjects with a history of severe allergies, non-allergic drug reactions, severe adverse reaction to any drug, or multiple drug allergies • Subjects with a hypersensitivity to the investigational drug, the control agent and/ or to inactive constituents • Presence or history of drug or alcohol abuse in the last 10 years, or intake of more than 21 units of alcohol weekly • Regular daily consumption of more than one liter of xanthine-containing beverages • Regular daily consumption of more than 5 cigarettes daily, or use more than 3 grams (1/8 ounce) of tobacco • Use of a prescription medicine during the 28 days before the first dose of trial medication or use of an over-the-counter medicine (with the exception of acetaminophen (paracetamol), during the 7 days before the first dose of trial medication • Use of dietary supplements or herbal remedies (such as St John's Wort) known to interfere with the CYP3A4 and/or P-gp metabolic pathways during the 28 days before the first dose of trial medication (see list in Study Procedures Manual) • Relevant pathological abnormalities in the ECG such as a second or third-degree AV block, prolongation of the QRS complex over 120 msec or of the QTc-interval over 450 msec (QTcB or QTcF) • Subjects testing positive in the drug screening • Excluded therapies which may impact on the interpretation of study results in the opinion of the investigator or sponsor • Objection by General Practitioner (GP) to subject entering trial • History of residing for 6 or more continuous months, within the last 3 years, in regions with endemic parasitic infections as determined by the investigator • Possibility that subject will not cooperate with the requirements of the protocol The following exclusion criteria are applicable only to subjects in Cohort 10: • No contact lenses wear within 1 month prior to dosing. Contact lenses wear is not permitted during the study. • Any ocular disorder for which topical ocular therapy is currently or

	chronically prescribed, including inflammatory eye disease (dry eye allergic conjunctivitis [seasonal allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis], uveitis and glaucoma) • Past history of ocular disease requiring ongoing treatment • Past ocular surgery including laser or other refractive corneal surgery • Evidence of eye irritation, visual difficulties, corneal opacity, ocular surface (corneal or conjunctival damage, with or without ocular symptoms) • Evidence of narrow anterior chamber angles causing increased risk of acute glaucoma • Evidence of ocular media opacity including lens opacity/vitreous opacities • Evidence of retinal or optic nerve pathology • Evidence of pronounced colour blindness, as indicated by an Ishihara score of 9/13 or below Subjects must not expose themselves to sunlight (eg, go out of doors) for longer than 15 minutes without using a strong sunblock (sun protection factor (SPF) 30 or above), or use a sunbed, or expose themselves to other sources of UV light, while they are taking emodepside and until 3 days after their last dose.
Removal of subjects from study	Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. Subjects who withdraw, or are withdrawn from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.
Safety Review	Safety will be reviewed throughout the study in Safety Review Meetings. Participants in the Safety Review Meeting will be at a minimum the Principal Investigator or his/her deputy and at least one Sponsor's representative (medically qualified). As an option, independent advisor(s) will be appointed, who will have access to unblinded data to advise if required (eg, on dose escalation decisions.)
Study Duration	Subject participation in the study will be for up to 7 weeks, including a screening phase (within 4 weeks prior to dosing), an in-house 1–week evaluation phase (Day -2 to Day 7), that will be followed by discharge on Day 7 for Options 1 and 2; with ambulatory evaluation visits scheduled as needed for Option 2 (up to maximally the follow-up visit on Day 21), or by a prolonged in-house evaluation phase (up to maximally Day 14) for Option 3, and a follow-up visit 3 weeks (+3 days) after dosing.
Rationale for Dose Selection and Route of	**Rationale for Starting Dose** The recommended starting dose in humans (70 kg) was calculated to be 1.75 mg/day (0.025 mg/kg), based on the following data:

Administration	28 days rats study: No Observed Adverse Effect Level (NOAEL) = 5 mg/kg ► Human Equivalent Dose (HED)+ safety factor 10 = 0.082 mg/kg 28 days dog study: NOAEL = 5 mg/kg ► HED + safety factor 10 = 0.27 mg/kg Dosages resulting in Margins of Safety of 10 from predicted human PK (unbound Cmax from dog scenario): - 28 days rats study: NOAEL = 5 mg/kg ► 0.048 mg/kg - 28 days dog study: NOAEL = 5 mg/kg ► 0.075 mg/kg - Single administration rat: NOAEL = 10 mg/kg ► 0.035 mg/kg 1.75mg is not practical to dose in the Liquid Service Formulation (LSF, solution), and it is not recommended to dose the LSF in less than 0.5mL (0.5mg) increments. 1mg is chosen as the starting dose. Two dose steps are required to reach the 5mg dose (tablet).
Rationale for Study Population	The study will be performed in healthy, male Caucasian volunteers. Currently there are no data to indicate that emodepside will be sensitive to ethnic factors, according to criteria in ICH Guideline E5 'Ethnic Factors in the Acceptability of Foreign Clinical Data'. As per the ICH E5 guidelines, knowledge of the pharmacokinetic and pharmacodynamic properties, and the translation of these to clinical efficacy and safety, are required to assess if emodepside will be sensitive to ethnic factors. Therefore data gathered in the current study will contribute to an evaluation of the need for a bridging study in other ethnic groups. However optionally, after further evaluation during the study, at the sponsor's discretion other ethnic groups may be recruited.
Sample Size:	Up to 80 subjects (up to 10 cohorts, each of up to 8 subjects).

Study Treatments	**Test-Drug:** Emodepside Liquid Service Formulation (LSF) solution or matching placebo solution; emodepside immediate release (IR) tablets of 5 and 20 mg or matching placebo tablets. **Part 1 Dose-Escalation:** 1st dose-level: 1 mg (solution); up to 8 subjects 2nd dose-level: 2.5 mg (solution); up to 8 subjects 3rd dose-level: 5 mg (solution); up to 8 subjects 4th dose-level: 5 mg (tablet); up to 8 subjects 5th dose-level: 10 mg (solution); up to 8 subjects 6th dose-level: 20 mg (solution); up to 8 subjects 7th dose-level: 20 mg (tablet); up to 8 subjects 8th dose-level: 40 mg (solution); up to 8 subjects **Part 2 Doses** 9th dose-level: 10 mg fed (solution); up to 8 subjects 10th dose-level: 40 mg (solution); up to 8 subjects Frequency of administration: Doses will be administered as a single oral dose to be taken while fasting. In addition, the 5 and 20 mg dose-levels will be repeated with 5 and 20 mg IR tablets (optional), in order to estimate the relative bioavailability of this formulation early, and for comparison within the same study. The IR tablet dose-levels will be inserted in the dose-escalation, depending on the availability of the IR tablets and the results of the respective doses (5 and 20 mg) administered as oral solution. The effect of food on the bioavailability of the emodepside LSF solution will be assessed in Cohort 9. Cohort 10 will be used to further characterize and assess the relationship between emodepside and adverse events seen in earlier cohorts, as long as those adverse events were of mild or moderate intensity and do not in any way threaten the health of the subject. This Cohort will be used to investigate in particular the effect of emodepside on the eye system. To accommodate the additional ophthalmology assessments that will be needed this cohort will have a reduced number of timepoints for other assessments compared to the previous cohorts. In this Cohort, emodepside or placebo will be administered as a single oral dose to be taken while fasting. Decision to escalate the dose will be taken during a Safety Review Meeting before each new dose step after reviewing safety data collected following study drug administration. Based on safety considerations, a reduction in dose is always possible, after review of safety and tolerability data from the previous dose step.
Statistics Sample size	For evaluation, a minimum number of 6 evaluable subjects per cohort is required.

Randomization	In each cohort of 8 subjects, 6 subjects will be randomised to receive emodepside and 2 subjects will be randomised to receive placebo. The sample size of up to 8 per dose step (cohort) is considered sufficient to examine the safety and tolerability of emodepside as well as the pharmacokinetics after single oral administration of the investigational drug. **Safety:** Safety and tolerability data will be summarized using the following parameters: • Vital signs; • 12-lead ECG; • Hematology; • Clinical chemistry; • Urinalysis; • Physical and neurological examination; • AEs. • Ophthalmology assessments (Part 2, Cohort 10) No formal hypothesis testing of these parameters will be carried out. **Pharmacodynamic:** Pharmacodynamic variables at each planned assessment, and change in pharmacodynamic variables from baseline at each planned post baseline assessment, will be summarised by actual treatment. **Pharmacokinetic:** PK concentration data will be summarised using the PK Concentration population. PK parameters will be summarised using the PK Parameter population. For log-transformed parameters, the primary measure of central tendency will be the geometric mean; for untransformed parameters, it will be the arithmetic mean or median. For all variables, N (number of subjects in receiving the treatment/formulation in the population), n (number of observations), arithmetic mean, median, minimum, maximum, SD, %CV, and the 95% confidence interval of the arithmetic mean will be derived. For log transformed variables, all of the above plus the geometric mean, its 95% confidence interval, and the SD of the log-transformed variables, will be provided. Optionally, the relative bioavailability of the IR tablet will be calculated: F_{rel} Plasma concentrations and PK parameters of emodepside and metabolites will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically. If concentrations of emodepside and its metabolites in urine are determined, the amount of emodepside excreted in the urine will be estimated.

1. Background and Study Rationale

1.1. Background Information

Filarial diseases cover infectious diseases caused by parasitic nematode worms onchocerciasis (river blindness), lymphatic filariasis (LF, or elephantiasis), and loiasis (African eye worm, or *Loa loa*). More than 1 billion of the world's poorest people are at risk.[24,25] An estimated 120 million people suffer from LF, and about 80% of people at risk live in the following 10 countries: Bangladesh, Democratic Republic of Congo, Ethiopia, India, Indonesia, Myanmar, Nigeria, Nepal, Philippines, and the Republic of Tanzania.[25] Loiasis occurs exclusively in West and Central Africa, where an estimated 13 million are infected with *Loa loa*.[12] An estimated 37 million[20] suffer from onchocerciasis, with 99% cases in 31 African countries, and 169 million at risk. Although the disease is almost exclusively confined to West and Central Africa, some foci exist in Yemen and South America (Brazil and Venezuela).[12,23]

The burden associated to onchocerciasis is estimated at nearly 600'000 disability-adjusted life years (DALYs) worldwide.[22] Severe visual impairment and blindness are considered the most severe complication of the disease and their control was the main objective of the initial control programs in West Africa (OCP). However skin lesion and itching represent a significant public health problem in affected communities. Incessant itching may cause insomnia, affects work productivity and social relationships and can even induce a premature child weaning by affected mothers.[1] Onchocerciasis is still the world's second-leading infectious cause of blindness. The World Health Organization (WHO) estimates that 746'000 patients are visually impaired, 265'000 are blinded and more than 4 million suffer from severe itching.[22]

Onchocerca is a helminth of the genus nematode (roundworm), causing onchocerciasis in humans. The disease is contracted through the bite of an infected vector, a female blackfly of the genus *Simulium*, which transmits infective larvae to a person. Once injected in the host, the larvae molt twice before reaching adult stage. An adult worm can then live for 15 years in the human body.[9] An adult worms settle into fibrous nodules in the human body close to the surface of the skin or near the joints. Adult male migrates from nodule to nodule. After mating, a female releases about 1,000 new microfilariae per day. The microfilariae migrate through the skin where they are eventually ingested by a blackfly in which the parasite completes its life cycle by molting twice into an infective larvae. These larvae may then be transferred to another host to continue the cycle.

Clinical Manifestations

Infection with *O. volvulus* can result in initial symptoms such as fever, neuralgic pain in joints, and temporary hives on the trunk and face. Pruritus is the most common early symptom of onchocerciasis. It usually develops after a latent or "prepatent" interval of 1 to 2 years following initial infection.[10] Some infected persons remain asymptomatic (about 10% of cases[9]) or can develop symptoms during the course of the infection (which last up to 14 years). Inflammatory responses due to dead or

dying microfilaria are responsible for the majority of the clinical manifestations, which can range from the dermatological to the ocular symptoms, briefly described below.

Dermatological Symptoms

Onchoceral Dermatitis is the most common symptom of the disease. The condition can appear anywhere on the body and usually begins with intense itching. A rash consisting of patches of papules can appear on the body at any time and often leads to incessant scratching. In West Africa, this condition is known as craw-craw. This acute dermatitis may progress into chronic dermatitis with large papules and, in a later stage, hyper-pigmentation and the thickening of the skin, popularly known as Lizard skin. More advanced stage is characterized by loss of elasticity, atrophy of the skin and depigmentation known as Leopard skin.[15]

Onchocercomas are subcutaneous, fibrous nodules where adult worms dwell and breed. These nodules are most easily felt when they form over a bony part of the body. The location of the nodules on the body depends on the place that the fly bites, which varies by region. In America, the nodules are mostly found on the upper body in the head and neck region, whereas in Africa the nodules are mostly on the lower body, especially in the groin region. It is estimated that only 30% of existing nodules can be found by palpation (95% CI 16-41%).[9]

Ocular Symptoms

Ocular symptoms are severe reactions that occur only after several years of having the disease. Initially, dead microfilariae in the eye cause inflammation and keratitis. Then, if the infection persists over a number of years, sclerosing keratitis, iridocyclitis, chorioretinitis, and uveitis occur, resulting in permanent visual impairment, glaucoma, or blindness. It is estimated that the life expectancy of a person who becomes blind in endemic areas may be shortened by up to 10 years.[19]

Diagnosis

Standard diagnosis of onchocerciasis is made by examination for microfilariae in skin biopsies. This technique has low sensitivity in light infections and it is an invasive method with low acceptability among the population. Infection in the eyes can be diagnosed with a slit-lamp examination to detect microfilaria and onchocerciasis lesions. In patients presenting subcutaneous nodules, adult worms can be found inside the nodules surgically removed. Other diagnostic methods are PCR-based diagnosis of skin scrapings for *O. volvulus*, more sensitive than parasitological examination of skin snips, and Ov-16 antibody detection card tests or diethylcarbamazine (DEC) patch test.

Treatment

Ivermectin (150 mg/kg single, oral dose) is the standard treatment of onchocerciasis patients. The drug kills the microfilarial stage of the parasite and includes temporary sterilization of adult female worm, reducing disease transmission and morbidity. However, the drug fails to kill adult worms, as a consequence, onchocerciasis requires treatments for up to 15 years (the life span of adult worms), to eliminate the parasite from the body.

Programs directed by the WHO for the treatment and control of onchocerciasis have been in place for over twenty years. The African Program for Onchocerciasis Control (APOC) spans 24 countries in Central and Western Africa. The treatment approach is preventive chemotherapy based on the administration of ivermectin once or twice a year to all the population in endemic areas.

In areas of Loa loa co-infection, serious adverse events (SAE) following the use of ivermectin were observed.[4,6] The most severe complication is an encephalopathy which is triggered by the massive death of microfilariae that can be fatal or leave long-term sequelae.[6] SAEs happen in 1 in 10'000 treatments among patients with high Loa loa parasitemia in Western and Central Africa (Angola, Cameroon, Democratic Republic of Congo, South Sudan) where onchocerciasis and loiasis are often co-endemic (The Mectizan Expert Committe and the Technical Consultative Committee, 2004).[18] Geographical areas in which prevalence of *Loa loa* is higher than 20% are considered as high risk for encephalopathy.[5] These areas have been defined through an epidemiological survey called Rapid Assessment Procedure for *Loa Loa* (RAPLOA).[17] In these areas the risk of SAEs is particularly high when mass drug administration (MDA) programs are implemented for the first or second time when microfilariae prevalence is highest within the treated population.

Rationale for the Development of Emodepside

The programs for the treatment and control of filarial diseases through MDA have been in place for over 20 years with an important success in reducing transmission and morbidity. However, current treatments must be repeated at regular intervals for the life of the adult worm (up to 15 years), making implementation extremely difficult in endemic countries.

Additionally, the programs have to be implemented with special measures in regions of Onchocerca infection where patients are co-infected with Loa loa. This limits the use of ivermectin in MDA programs in co-endemic areas, and is an impediment to achieving WHO elimination goals for onchocerciasis. Furthermore, reports of a suboptimal parasite response to ivermectin may be a sign of developing resistance.[16]

Thus, there is an urgent need for a macrofilaricide, targeting onchocerciasis worms for use in individual case management and, after appropriate testing, as an alternative treatment in MDA programs. A macrofilaricidal drug could reduce the number of MDA cycles needed thereby easing program implementation and enhancing chances of disease elimination, particularly in Loa loa co-endemic areas.

Emodepside (synonym: BAY 44 4400) is a cyclooctadepsipeptide anthelmintic drug stimulating presynaptic receptors belonging to the secretin receptor family, resulting in flaccid paralysis of parasitic nematodes. Emodepside also interacts with SLO-1, a calcium activated potassium channel. Emodepside is a registered drug for animal health, commercialized by Bayer Health Care under the name of Profender® (in combination with praziquantel) or Procox® (in combination with toltrazuril) indicated for treatment of *Toxocara cati*, *Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala*, *Trichuris vulpis* and *Ancylostoma tubaeforme* infections. Emodepside is a semi-synthetic drug with the precursor isolated as fermentation products from *Mycelia sterilia*, a fungus that grows on leaves of *Camellia japonica*.

Emodepside was shown to be macrofilaricide against a variety of filarial nematodes as investigated in both in vitro and in vivo studies: *Achatocheilonema viteae*, *Litomosoides sigmodontis*, *Brugia malayi*, *Onchocerca gutturosa*, *Onchocerca lienalis*. These filarial models are the accepted models for filarial diseases in humans.[3]

In conclusion, emodepside targets different life stages of helminths parasites including the adult stage. This is a very important feature since treatments targeting *Onchocerca* adult worms have the potential to eliminate infection. Hence, emodepside can be considered as promising drug candidate able to fulfill unmet medical needs for the treatment of onchocerciasis.

There are currently no drugs targeting the adult stage of *Onchocerca* parasites in humans. Therefore the clinical development plan will consider a number of clinical endpoints to assess the effect of emodepside in humans.

1.2. Summary of Non-Clinical Information

An extended battery of nonclinical studies supported the marketing of emodepside as a veterinary drug. To support the clinical development of emodepside in healthy volunteers and patients suffering from river blindness, additional studies have been performed to ensure all requirements for administration in man are met.

Pharmacology

A surrogate filarial nematode species was used (*Litomosoides sigmodontis*) which represents a permissive disease model considered to be a reasonable predictor for *Onchocerca volvulus* infection. A comprehensive set of primary pharmacodynamic studies was performed to characterize and assess the efficacy of emodepside against different filarial nematode species. Emodepside was capable of reducing the motility of both adult worms and microfilariae in *L. sigmodontis* in vitro with a minimum inhibitory concentration (MIC) close to 0.1 µM (111.9 ng/mL). The MIC is defined as the minimum concentration inhibiting the worm's motility completely. *In vivo* Balb/c mice and jirds, a well-established, anthelmintic rodent model, were naturally infected with *L. sigmodontis* and treated with emodepside at different doses and formulations. In these studies treatment with emodepside efficiently and dose dependently reduced number of adult parasites.

A large number of safety pharmacology studies were performed in vitro (+ mechanistic studies) and in vivo in rats and dogs. In addition, standard safety pharmacology parameters were included in the toxicity studies with emodepside in rats and dogs.

Secondary pharmacology studies did not detect any off-target receptor binding at clinically relevant concentrations. The in vitro hERG assay showed no critical potential for QT prolongation (IC20 19 µM).

Safety pharmacology and repeated dose toxicity studies revealed the central nervous system as a target organ with changes in behavior, activity, tremor and gait abnormalities in rats, mice and dogs. A No Observed Adverse Effect Level (NOAEL) of 5 mg/kg i.d. was defined in dogs and rats after repeated administration (4-week repeat oral dose toxicity study). 10 mg/kg body weight was established as NOEL for effects on the nervous system in fasted rats after acute administration.

After a single oral application of emodepside to rats no biologically relevant effect on respiratory parameters was noted (10-100 mg/kg bodyweight [bw]). Also in dogs, no effect on respiratory functions was observed at the tested doses. Hyperglycaemia was observed in rats in acute and repeated dose studies. Fasted rats were less sensitive with a NOEL of 10 mg/kg body weight compared to fed rats with a NOEL of 1 mg/kg body weight. Mechanistic studies showed that emodepside inhibited secretory activities in mouse and rat β-cells of the pancreas presumably consistent with a mode of action through secretin receptors.

Emodepside showed no adverse effect on the ECG in anesthetized dogs. However, a moderate vasodilatation (reduction of total resistance, slight decrease of arterial blood pressure, moderate, probably reflex tachycardia) was observed at ≥1.5 mg/kg bw. A threshold plasma level of 0.1 µg/mL was determined for this effect. The significance of the vasodilatory effects is unclear as no effect on blood pressure or heart rate was seen in dogs following oral administration of emodepside for 4 weeks at up to 20 mg/kg bw.

Absorption, Distribution, Metabolism, Excretion (ADME)

In vitro studies showed moderate plasma protein binding of emodepside in all tested species with similar values in mice, dogs and human (fu 1.0 – 1.6%). In rats, gerbils and rabbits the fraction unbound was slightly higher (2.7% - 3.1%). The relevant Phase 1 biotransformation pathways of emodepside in humans as well as in animal species were oxidation with no significant species differences in terms of metabolic pathways. In humans, oxidative metabolism of emodepside was predominantly catalyzed by CYP3A4. The hydrolysis of the ester bonds was observed as an additional metabolic clearance pathway. Transport studies revealed a high permeability of Caco2-cells to emodepside as well as active efflux which was characterized as being P-glycoprotein mediated. Therefore, a role for P-glycoprotein in the pharmacokinetics of the compound cannot be excluded.

Single dose pharmacokinetics (PK) of emodepside was studied in rats, and dogs after single intravenous (i.v.) and oral (p.o.) administration. The absolute bioavailability of emodepside was moderate in rats and dogs with 44% and 52%, respectively. Plasma clearance was low in rats (0.77 L/[kg·h]), and dogs (0.30 L/[kg·h]). The volume of distribution was high in both species with 8.5 in dogs and 38.7 l/kg in rats. The plasma elimination half-life was 33 to 43 hours in rats and 42 to 35 hours in dogs after p.o. and i.v. administration, respectively.

Biodistribution studies with 14C-labeled emodepside in rats, revealed a moderate to high affinity to most tissues and organs after p.o. administration (1 or 15 mg/kg) with higher concentrations in tissues than in the blood. The highest proportion of emodepside was found in brown and white adipose tissue, the liver and adrenals. There was also a low penetration of the blood-brain barrier. The distribution patterns were similar in both sexes.

The main excretion pathway after oral administration in rats was the fecal/biliary route (about 50% within 24 h, 83–93% within 168 h), with only 2-3% of the dose being found in urine. The unchanged compound emodepside accounted with 45-56% for the majority of the dose excreted into feces. The major metabolites in feces

were identified as the hydrolysis product, its dehydrated and oxidized derivatives as well as three oxidized metabolites.

After repeated oral dosing of 14C labeled emodepside in rats, the parent compound was the major component found in rat plasma with a small amount of metabolite M 1 detected in rat plasma.

Toxicokinetic (TK) data were obtained from GLP 4-week repeated dose studies in rats and dogs. In rats exposure was slightly less than dose-proportional after oral administration. In dogs, the toxicokinetics showed a more than dose proportional increase in $AUC_{0\ 24h}$ and C_{max} (5 – 20 mg/kg).

Toxicology

A comprehensive battery of repeated dose studies was conducted, in which emodepside was orally applied (in diet) for up to 13 and 14 weeks in mice and rats, respectively, at doses up to 1000 ppm and 800 ppm (1000 ppm equals in mice approx. 245-380 mg/kg bw, 800 ppm equals in rats approx. 77-95 mg/kg bw, both in 13-week treatment schedule).

The studies in rats revealed toxicities resulting from metabolic changes induced by emodepside indirectly, such as a decrement in bodyweight gain but in parallel an increased feed and water consumption as well as deformation of teeth as a sign of a diabetic-like effect. The main affected organs were kidney, pancreas and liver, with associated changes in hematological parameters, triglyceride and glucose levels in the plasma and lipid and glycogen stores. These toxicological findings pointed to a diabetes-related condition (inhibition insulin secretion followed by increased glucose levels, reduced leptin levels, as confirmed by mechanistic studies). In mice, the NOAEL after 14 week of treatment was 50 ppm (10.5-16.8 mg/kg bw.). The NOAEL in the 14 week rat study was defined at 10 ppm (m: 0.73, f: 1.11 mg/kg bw per day); In 4-week rat studies 50 ppm (equals 4 – 5 mg/kg bw) was defined as NOAEL.

In dogs, doses starting from 10 mg/kg bw per day for 4 weeks resulted in clinical signs like vomiting, tremor and unsteady gait. At 20 mg/kg bw, an effect on nutritional state, food intake and bodyweight gain was noted. All effects were reversible after a recovery period of 4 weeks. The NOAEL for this study was 5 mg/kg bw.

Several reproductive and developmental toxicity studies were conducted in rats and rabbits. Effects of emodepside on the reproductive performance in rats occurred only at parentally toxic doses. No primary effect on fertility and reproduction was observed. In this species, both ovarian weight and gestation rate were unaffected by treatment. Primary systemic parental effects were due to diabetes I like effects, which were well known from repeat dose studies in rats. A battery of well-conducted, GLP-compliant teratogenicity studies revealed maternal toxicity, foetotoxicity, foetal malformations and various skeletal/visceral anomalies or deviations. Clinical signs of systemic maternal toxicity were evident at dose rates ≥6 mg/kg bw. Overall, severe maternal toxicity at 18 mg/kg bw resulted in adverse effects on foetal development. The NOAEL for maternal toxicity in rats was 2 mg/kg bw and the NOAEL for developmental toxicity was 0.5 mg/kg bw. However, as discussed above, diabetes like effects, which were not measured in developmental toxicity studies, occurred in lower dosages. Therefore, it can be assumed that the maternal toxic dose was

significantly lower (NOEL of 1 mg/kg bodyweight in safety pharmacology studies on glucose levels in the blood. See also glucose level in pregnant rats). In rabbits, the effects were similar to the rat studies. The NOEL for developmental toxicity in the rabbit was 5 mg/kg bw.

Additional endocrinology studies confirmed the involvement of emodepside in hormone deregulation (reduced E2, T3, insulin, leptin and prolactin levels and enhanced TSH and glucagon levels) while not having estrogenic/anti-estrogenic or androgenic/ anti-androgenic potency. This deregulation is assumed to be the cause for the observed developmental toxicity.

In vitro and in vivo genotoxicity studies revealed no mutagenic potential for emodepside; no carcinogenicity studies were conducted. Local tolerance studies in rats and rabbits revealed no skin- or eye-irritating potential of emodepside. In guinea pigs, emodepside was found to have no skin sensitization potential.

1.3. Summary of Human Clinical Information

Before this study, no human clinical trials had been conducted with emodepside. In this First–in–Human (FIH) trial (Part 1, Cohorts 1-8), the safety of emodepside is being tested in healthy volunteers (Clinical Phase 1).

To date, a total of 71 healthy male volunteers have been exposed to emodepside (dose range 1.0 mg–40 mg LSF solution, and dose range 5 mg-20 mg tablet) or placebo (in this study (unblinded data available from Cohorts 1-8 [n=63 subjects]).

Maximum exposure was observed with the 40 mg LSF solution (Cohort 8), with a mean C_{max} of 612 ng/mL and AUC of 4315 ng.h/mL. So far, based on unblinded safety data from Part 1 (cohorts 1-8), those doses have been safe and tolerance was acceptable (see Table 1).

Across all treatments within Part 1 (cohorts 1-8), no serious adverse events were reported. The majority of Treatment Emergent Adverse Events (TEAEs) experienced were mild in severity (22 subjects [34.9%] versus 9 subjects [14.3%] who experienced events of moderate severity). A total of 14 subjects (22.2%) experienced 20 TEAEs that were considered by the investigator to be related to emodepside treatment.

Across all treatments, the most frequent treatment-related TEAEs occurred within the System Organ Classes (SOCs) of eye disorders and nervous system disorders (8 subjects [12.7%] within each SOC, respectively). After a single fasted dose of 40 mg LSF solution (Cohort 8), 4 subjects (66.7%) reported at least 1 TEAE of blurred vision (of mild severity), and 2 subjects (33.3%) reported at least 1 TEAE of impaired vision (of mild severity). In the 20 mg LSF group, 1 subject (16.7%) experienced a TEAE of blurred vision of mild severity, and no subjects (0%), reported visual impairment which is indicative of a dose-dependent trend. Those TEAEs resolved spontaneously within 24 hours without treatment, caused no discomfort to the subjects and there were no lasting effects upon ophthalmology review. As per Section 7.4 of the protocol, in the occurrence of mild or moderate intensity adverse events which do not in any way threaten the health of the subject, that dose level may be repeated with the aim of exploring further the relationship between dose and adverse event. Cohort 10 in Part 2 will be used to further explore the effect of emodepside on the eye system.

One subject (of 63 exposed to emodepside or placebo during cohorts 1-8) in Cohort 1 (1 mg solution) was found to be ineligible due to a pre-treatment event, of prolonged pre-dose PR interval. The event was noted by the Investigator at the moment of dosing. Dosing was stopped immediately but the subject received 0.1 mg of emodepside. The event was not serious, was neither treatment-emergent nor related to study treatment, and was mild in severity. The subject was withdrawn from the study. Overall, tolerability of emodepside has been good to date.

Table 1 Treatment-emergent drug-related adverse events reported by 2 or more subjects in any individual treatment group in Part 1 (Cohorts 1 to 8): Safety population

System Organ Class / Preferred Term	Placebo		Emodepside								All Subjects
			1 mg	2.5 mg	5 mg	5 mg	10 mg	20 mg	20 mg	40 mg	
	LSF	IR	LSF	LSF	LSF	IR	LSF	LSF	IR	LSF	
	N=12 n (%)	N=4 n (%)	N=5 n (%)	N=6 n (%)	N=6 n (%)	N=6 n (%)	N=6 n (%)	N=1 n (%)	N=6 n (%)	N=6 n (%)	N=63 n (%)
Eye disorders	**0**	**0**	**0**	**0**	**0**	**0**	**2 (33.3)**	**1 (16.7)**	**0**	**5 (83.3)**	**8 (12.7)**
Vision blurred	0	0	0	0	0	0	0	1 (16.7)	0	4 (66.7)	5 (7.9)
Photophobia	0	0	0	0	0	0	2 (33.3)	0	0	0	2 (3.2)
Visual impairment	0	0	0	0	0	0	0	0	0	2 (33.3)	2 (3.2)
Nervous system disorders	**1 (8.3)**	**0**	**1 (20.0)**	**0**	**1 (16.7)**	**0**	**1 (16.7)**	**1 (16.7)**	**0**	**3 (50.0)**	**8 (12.7)**
Dizziness	0	0	0	0	1 (16.7)	0	0	1 (16.7)	0	2 (33.3)	4 (6.3)

Subjects with ≥1 adverse event are counted once per system organ class and preferred term.

The pharmacokinetic results obtained so far show that T_{max} for the LSF solution is consistently about 1 h post-dose when fasted. Mean C_{max} and AUC for the LSF solution has been roughly dose-proportional with low to moderate inter-individual variability. The dominant half-life ($t_{1/2\ 0\text{-}24\ h}$) is estimated at approximately 11 h, and the terminal half-life ($t_{1/2\ 0\text{-}\infty}$) is approximately 500–700 h.

Relative bioavailability of the tablet formulation was about 35% for 5 mg and about 12% for 20 mg. Due to the lower bioavailability at the higher dose level, the LSF formulation will be used within the exploratory cohorts (Part 2 Cohort 9 and Part 2, Cohort 10). The results of PK analysis will be fully reported within the Clinical Study Report when the data is available from all cohorts.

Dose- and plasma concentration-dependent changes in insulin (decrease) and glucose (increase) levels were observed between 0 and 12 hours, with changes becoming apparent at dose levels of 10 mg LSF solution and above, in all subjects who received emodepside. No change in insulin or glucose levels was considered clinically significant by the investigator or to be an AE. The maximum glucose level reached in any subject was 12.7 mmol/L at 2 h post-dose at the 40 mg LSF solution dose level. No noticeable changes in cortisol, leptin or prolactin levels occurred and glucagon variations on pre and profile day did not show any particular trend.

1.4. Assessment and Management of Risk

Emodepside has never been given to humans before, so a sentinel dosing approach will be used at the first dose level. The dose in Cohort 1 will first be given to 2

sentinel subjects and the remaining subjects will not be dosed until at least 23 h later following review of available safety and tolerability data. To maintain the blinded nature of the study, the sentinel subjects will be randomized in a 1:1 ratio to receive emodepside:placebo.

Subjects in the FiH study (Part 1, Cohorts 1-8) and part 2 cohort 9, will remain hospitalized and will be closely monitored during the 7 days after their dose. A Safety Review Group (SRG) will be set-up to review any safety signal.

Part 2, Cohort 10:

The previous version of the protocol (version 4.0, dated 05 October 2016) included an additional optional cohort (Cohort 10). This cohort will be included, in order to explore in detail the effect of emodepside on the eye system using a dose level that was already completed in a prior cohort (see Section 1.3). Therefore this cohort is exploratory in nature, and is not considered to be FIH because it will repeat a dose level already tested in Part 1 of the study. Subjects will be transported to an eye hospital for ophthalmology assessments approximately 2-2.5 h post-dose and then transported back to the phase 1 unit, otherwise subjects will remain hospitalized in the phase 1 unit for 7 days consecutively following the single dose. Subjects could potentially be off-site (at the eye hospital) during or after the expected T_{max}, however they will be under the direct medical supervision of a physician and nurse from the phase 1 unit at all times (including transportation). A dose of 40 mg LSF solution was previously tested in Part 1, Cohort 8, and the safety and tolerability profile was found acceptable.

As Part 1 of this study is considered FIH, before a subject can be dosed in Part 1 (Cohorts 1-8) a General Practitioner (GP) reply must be obtained, or a valid GP reply must be on file.

As the doses to be tested in Part 2 (Cohorts 9 and 10) will have already been tested within this study; those cohorts are not considered FIH. For those cohorts, subjects' GPs will be contacted but a reply is not required prior to dosing.

Any safety risk to study participants is mitigated by the following considerations:

Emodepside is registered as veterinary product worldwide. Therefore, a complete toxicological package is available which also covers human requirements.

It is shown in a set of genotoxicity studies that emodepside is not genotoxic. Additionally, developmental toxicity studies in rats and rabbits showed that emodepside had no teratogenic or primary embryo/ fetotoxic potential. However, contraception will be used during the study in accordance with MHRA request and HMR standard procedures (see Section 4.3 on Dietary and Lifestyle Guidelines).

Based on the nonclinical safety data, the toxicological release conference gave the following recommendations for the first in men study:

- The recommended starting dose in humans (70kg) is 1.75 mg/day.

- Monitoring of standard parameters, including blood pressure, glucose homeostasis (glucose, insulin, glucagon). Increased glucose levels and decreased insulin and glucagon levels have been observed in the non-clinical safety studies.

- Once the dose escalation is approaching plasma concentrations which were pre-clinically associated with CNS effects, particular attention should be given to observations/investigations indicating prodromal signs of tremor and incoordination.

- Due to missing data on phototoxicity clinical trial participants should avoid exposure to excessive sunlight

- Strong CYP3A4 inducers and inhibitors as well as co-medications that are relevant substrates for CYP3A4 should be excluded or closely monitored until the drug-interaction potential has been assessed in more detail.

- Strong P-gp inhibitors as well as co-medications that are relevant substrates for P-gp should be excluded or closely monitored until the drug-interaction potential has been assessed in more detail.

- The potential of emodepside to inhibit CYP3A4 and P-gp has to be further assessed clinically once it becomes clearer which emodepside exposure will be achieved at the therapeutic dose in humans.

The NOAEL of emodepside in dogs was $AUC_{(0-24)}$ 860 µg·h/L, C_{max} 175 µg/L, after 1 week at a dose level of 5 mg/kg. This dose resulted in an exposure after 4 weeks of $AUC_{(0-24)}$ 1611 µg●h/L, C_{max} 238 µg/L.

The maximal dose tested in dogs was 20 mg/kg. This dose resulted in an exposure after 4 weeks of $AUC_{(0-24)}$ 15887 µg●h/L, C_{max} 1682 µg/L.

(Note: The recommended starting dose in humans (70kg) is 1.75 mg/day, however for technical reasons (see Section 3.3) the dose of 1.0 mg is chosen as the starting dose)

2. Study Objectives and Endpoints

2.1. Primary Objectives

- To investigate the safety and tolerability of emodepside (BAY 44-4400) after single oral doses administered as solution or immediate release (IR) tablets in healthy male subjects.

2.2. Secondary Objectives

- To investigate the pharmacokinetics (PK) of emodepside (BAY 44-4400), after administration as oral solution, or IR tablet (optional).

- To conduct an exploratory investigation of the relative bioavailability of the 5 mg and 20 mg IR tablet formulation using data generated in this study (optional).

- Possibility to determine the effect of food on the bioavailability of emodepside (BAY 44-4400) after single oral doses administered as solution or IR tablets.

2.3. Study Endpoints

2.3.1. Safety and Tolerability Variables:

- Adverse Events (AEs),
- Physical and Neurological examination findings (including assessments of alertness, speech, language, and comprehension; cranial nerves; motor exam; coordination/cerebellar function; tremor of the hands, legs and head (postural, kinetic and rest tremor); sensation; and gait and postural stability (Pull test); mood; and sleepiness.)
- Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP) in supine and sitting position (Part 2, Cohort 10 only in supine position), weight, body mass index (BMI; height at screening only), oral temperature.
- 12-lead ECG (HR, PR, QRS, QTcF), and for selected cohorts 12-lead ECG continuous recording (for emodepside exposure response analysis - HR, PR, QRS and QTcF)
- Clinical laboratory parameters:
  Hematology: hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocytes, white blood cells (WBC) differential, red blood cells (RBC), glycated haemoglobin (HbA1C) (at screening);
  Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT)
- Biochemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), gamma-glutamyl transpeptidase (GGT), LDH, CK, amylase, lipase, free T4 and T3, thyroid-stimulating hormone (TSH), glucose, cholesterol (high-

density lipoprotein [HDL], and low-density lipoprotein [LDL], total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium in serum;
Urinalysis: by dipstick - glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites;.

- Ophthalmology assessments (Part 2, Cohort 10, only).

2.3.2. Pharmacokinetic Variables:

Based on the plasma concentration time data (collected after administration of oral solution, or IR tablet), the following PK parameters will be calculated, and compared between the 2 different administrative forms of emodepside.

- Main PK parameters: AUC_{∞}, AUC_{∞}/D, C_{max}, C_{max}/D of emodepside (BAY 44-4400)
- Exploratory PK parameters: $C_{max,norm}$, T_{max}, $t_{½}$, MRT, CL/F, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$, V_z/F of emodepside (BAY 44-4400)
- Other parameters: λ_z, $AUC_{t-\infty}$, points terminal

Optionally, the relative bioavailability of the IR tablet will be calculated: F_{rel}

The following PK parameters of metabolites of emodepside may be calculated: $AUC_{\infty,}$, $AUC_{\infty,}/D$, C_{max}, C_{max}/D, $C_{max,norm}$, T_{max}, $T_{½}$, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$.

In urine, the amount and concentration of emodepside and possibly its metabolites will be measured. The appropriate specific PK parameters to be calculated will be decided according to the concentration.

2.3.3. Pharmacodynamic Variables:

- Profiles of glucose and insulin (Parts 1 and 2, all cohorts), and glucagon and cortisol (Part 1 and Part 2, Cohort 9 only), only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1.
- Part 1 and Part 2, Cohort 9 only – Single samples of prolactin and leptin, only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1 (Part 1 and Part 2, Cohort 9 only).

3. Study Design and Study Design Rationale

3.1. Study Design

This will be a single-center, blinded, randomized, placebo-controlled, parallel-group, single-dose, 10-cohort, dose-escalation, comparison study investigating safety, tolerability, and PK of emodepside, after administration as oral liquid service formulation (LSF) solution in healthy male subjects (Figure 1).

The study is divided into 2 parts; Part 1 (Cohorts 1-8) is considered the FIH, single ascending dose phase of the study, where subjects will receive a single oral fasted dose, and which includes different formulations to allow assessment of relative

bioavailability. Part 2 is considered exploratory and will involve doses already tested in Part 1, so it is therefore not considered to be FIH.

Part 1 (Cohorts 1-8)

Optionally, a single dose of a 5 mg and 20 mg immediate release (IR) tablet formulation (Cohort 4 and Cohort 7, respectively) will be tested, subsequently to the completion of the respective dose steps of the single-dose escalation with oral solution (Cohort 3 and Cohort 6, respectively).

Because emodepside has never been given to humans before, the first dose will be staggered. Two leading subjects will be dosed no later than the day before the remaining subjects in Part 1, Cohort 1 will be dosed. To maintain the blind nature of the study, it will be ensured that 1 of the leading subjects, and 1 of the remaining subjects, are randomized to receive placebo.

Part 2 (Cohorts 9 and 10)

The effect of food on the bioavailability of the emodepside LSF solution will be assessed in Cohort 9.

Cohort 10 will be used to further characterize and assess the relationship between emodepside and adverse events seen in earlier cohorts, as long as those adverse events were all of mild or moderate intensity and do not in any way threaten the health of the subject. This Cohort will be used to investigate the mechanism by which emodepside may cause eye disorders. To accommodate the additional ophthalmology assessments that will be needed this cohort will have a reduced number of timepoints for other assessments compared to the previous cohorts (see Schedule of Events, Table 5 and Section 8).

The study will be performed in a single site specialized in Phase 1 studies. For each subject the study starts with the Screening Visit, which can be up to 4 weeks before the profile day (dosing). For eligible subjects, admission to the ward will be at latest the evening before the Pre-Day (Figure 2). One dose step per subject consists of one Pre-Day, one Profile Day and an in-house observation period of 7 days after administration of test substance.

Subjects will be discharged from the study ward 7 days after administration of test substance provided there are no medical objections (Day 7) – “Option 1” in Figure 2.

Figure 1- Study Design Overview

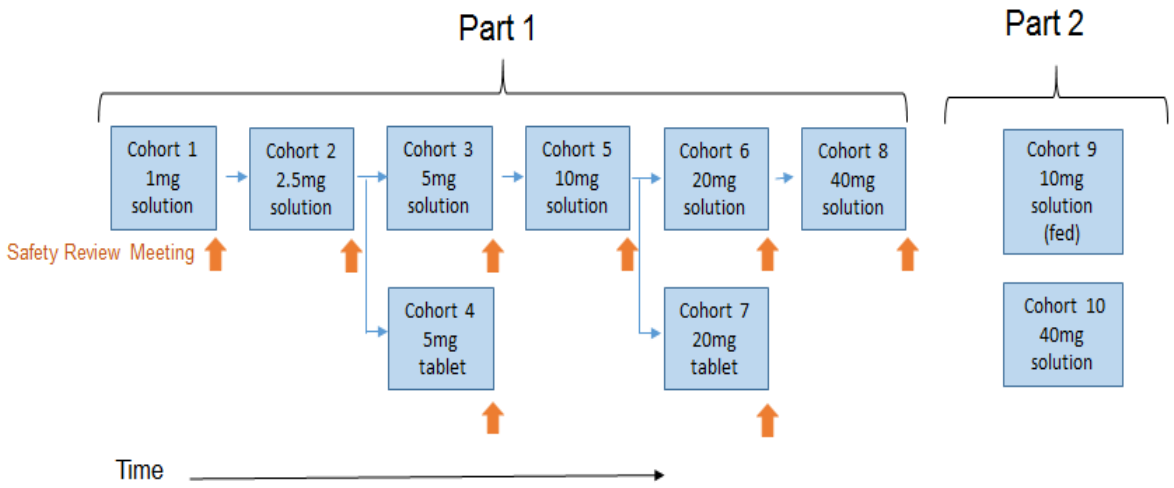
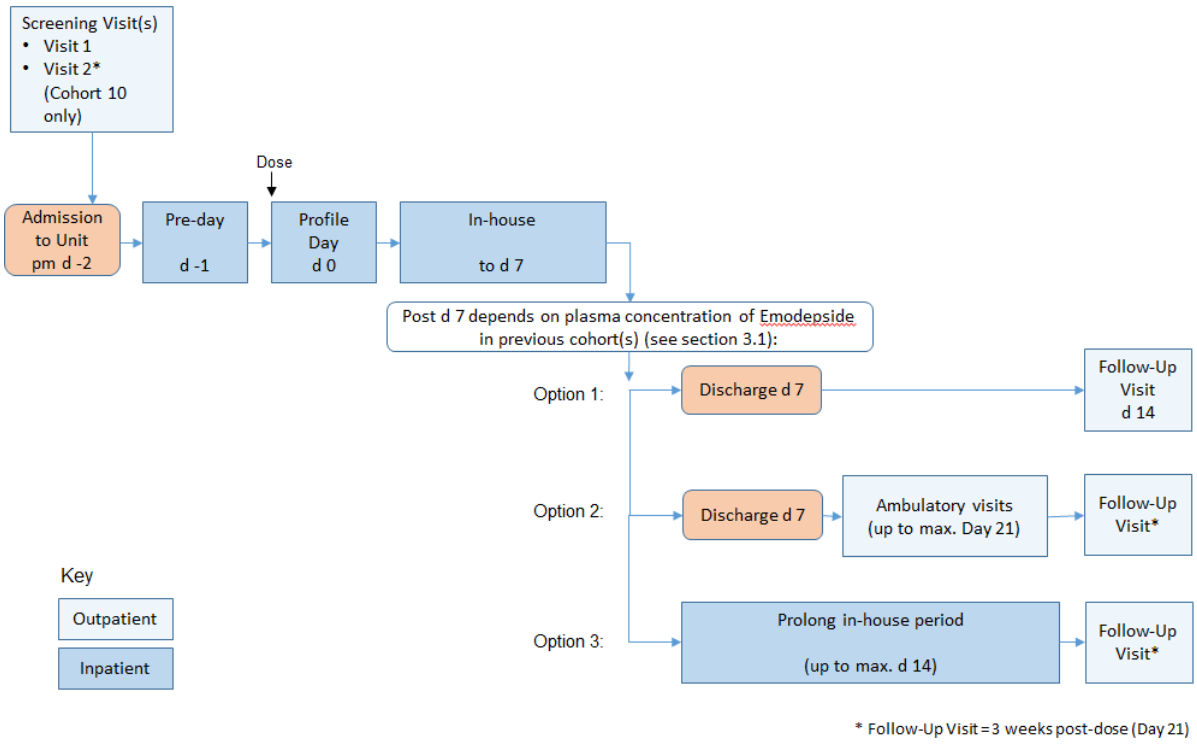


Figure 2- Parts 1 and 2: Study Flow Chart – Subject Level



*If eligible for study entry based on Screening Visit 1, subjects to be included in Part 2 Cohort 10 will have a second Screening Visit in order to undergo an ophthalmology assessment (within 7 days prior to Profile-Day [Day 0]) or on Pre Day at the latest.

However, if it is observed that **mean half-life of emodepside in any cohort** is longer than expected from the preclinical PK, and plasma concentrations of emodepside are still present 7 days after dosing, 2 alternative options may be employed to follow subjects after Day 7 (Figure 2) from Cohort 5 onwards and for all

subjects in **subsequent cohorts** (this decision will be made during Safety Review Meeting(s) – Section 11):

- Option 2: addition of up to 4 out-patient visits with measurements for safety and blood samples for PK over a period up to an additional 14 days (ie, up to follow-up on Day 21); or

- Option 3: prolongation of the in-house period for up to an additional 7 days (ie, up to Day 14) with additional measurements for safety and blood samples for PK taken on up to 4 days during that period.

Cohort 9 will follow option 2, (up to 4 visits during the period from Day 8–21 inclusive, as needed) and Cohort 10 will have outpatient visits on Days 10, 14 and 18.

In all cases, approximately three weeks after their dose of study medicine the subjects will undergo their final examinations in a Follow-Up Visit.

The end of the trial is defined as the final follow-up visit by the last subject (or final contact with the subject if that is later). If the trial is terminated early, the trial ends when the sponsor notifies the investigator in writing that the trial has finished, or when the last subject attends the final follow-up visit, whichever is later. The Study Schedule of Events is provided in Table 3 (Part 1 and Part 2, Cohort 9) and Table 5 (Part 2, Cohort 10) and Table 4 (Section 5) provides a detailed overview of all study procedures, which is further discussed in Section 8 Study Procedures.

3.2. Study Duration and Duration of Subject Participation

Subject participation in Parts 1 and 2 of the study will be for up to 7 weeks, including a screening phase (within 4 weeks prior to dosing), an in-house 1-week evaluation phase (Day 1 to Day 7), that will be followed by discharge on Day 7 for Options 1 and 2 (Figure 2, Table 4; with ambulatory evaluation visits scheduled as needed for Option 2 [up to maximally the follow-up visit on Day 21]), or by a prolonged in-house evaluation phase (up to maximally Day 14) for Option 3, and a follow-up visit three weeks (+3 days) after dosing (Figure 2, Table 3, Table 4).

3.3. Rationale of Study Design and Dosing

This study applies a standard Phase I single dose escalation design. The data from this Single Ascending Dose study will be used to design subsequent Phase I studies of emodepside (eg, additional food effect and multiple ascending dose studies.)

The study will be performed in healthy male Caucasian volunteers. Currently there are no data to indicate that emodepside will be sensitive to ethnic factors, according to criteria in ICH Guideline E5 ‘Ethnic Factors in the Acceptability of Foreign Clinical Data’. As per the ICH E5 guidelines, knowledge of the pharmacokinetic and pharmacodynamic properties, and the translation of these to clinical efficacy and safety, are required to assess if emodepside will be sensitive to ethnic factors. Therefore data gathered in the current study will contribute to an evaluation of the need for a bridging study in other ethnic groups. However optionally, after further evaluation during the study, at the sponsor’s discretion other ethnic groups may be recruited.

The study is performed in a blinded design, in which the subjects and the study personal (investigators and nurses) are blinded, in order to avoid bias in the collection and evaluation of data in its conduct. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

The decision about dose escalation will be taken in the Safety Review Meeting, prior to dosing of the subsequent cohort (see Section 7.4).

The rationale for the 7 day in-house period is based on an assumed dominant half-life of emodepside of 36 hours, derived from pharmacokinetics in dog and rat after oral administration. Applying the convention of in-house stay corresponding to 5 half-lives: 36h x 5 = 180h, equivalent to 7.5 days. However this may be extended if subjects have relevant plasma concentrations in early dose steps.

The 7 day Follow-Up Visit is scheduled according to standard practice for this type of study.

The recommended starting dose in humans (70 kg) was calculated to be 1.75 mg/day (0.025 mg/kg), based on the following data:

- 28 days rats study: No Observed Adverse Effect Level (NOAEL) = 5 mg/kg ► Human Equivalent Dose (HED) + safety factor 10 = 0.082 mg/kg
- 28 days dog study: NOAEL = 5 mg/kg ► HED + safety factor 10 = 0.27 mg/kg

Dosages resulting in Margins of Safety of 10 from predicted human PK (unbound C_{max} from dog scenario):

- 28 days rats study: NOAEL = 5 mg/kg ► 0.048 mg/kg
- 28 days dog study: NOAEL = 5 mg/kg ► 0.075 mg/kg
- Single administration rat: NOAEL = 10 mg/kg ► 0.035 mg/kg

The 1.75 mg dose is not practical in the Liquid Service Formulation (LSF, solution), and it is not recommended to dose the LSF in less than 0.5 mL (0.5 mg) increments. The dose of 1.0 mg is chosen as the starting dose. Therefore, two dose steps are required to reach the 5 mg dose (tablet).

Estimation of Human Exposure to Emodepside

The prediction of human PK was based on the data obtained from in vivo experiments after administration of emodepside to rats and dogs and from in vitro data (plasma protein binding, blood/plasma partitioning).

The classical allometric species scaling approach (with fu correction) including both species resulted in implausible values for the exponent for both CL and V_{ss}. Therefore, the key parameters CL and Vss were assessed by single species scaling.

In order to predict human PK parameters and c/t profiles, rat and dog plasma concentrations after intravenous and oral administration were fitted to a 3 compartment model using Phoenix 6.3. In order to obtain a better fit the 96h values of the rat PK data were excluded. Fitted single parameters for CL, CLD1, CLD2, Vc, Vt1 and Vt2 were scaled to humans considering fu and using the fixed exponent approach with an exponent of 1 for scaling of volumes and 0.75 for scaling of clearances. The bioavailability used for the prediction of the oral concentration vs. time profiles in man was with 50% about the mean value from bioavailabilities observed in animal species.

The predicted human CL is low for both species used for prediction. The differences in predicted human clearance ranging from 0.11 (rat) to 0.14 L/(kg·h) (dog) are minor. With the Cb/Cp distribution of 0.6 values for CLblood would be 0.18 (rat) and 0.23 (dog), respectively. These predictions are in the same range as the human clearance obtained in vitro in hepatocytes (CLblood = 0.36 L/(kg·h)). The predicted volume of distribution in man is high covering a range of 15 L/kg (rat) to 11 L/kg (dog). However, individual parameters for volume (Vc, Vt1 and Vt2) showed differences according to the species used for prediction. Consequently, the C/t profiles predicted for man mainly differ in C_{max} and t_{max}. The value for the absorption rate constant (ka, 0.8 h-1) was based on former experiences with PEG-based liquid service formulations. The bioavailability obtained from the animal species was directly used for the prediction of the human plasma concentration profiles.

Description of the theoretical dose levels to be studied is presented in Table 2:

Table 2. Study Treatment: Formulation and Dose-Levels by Cohort

Part	Cohort	Formulation	Dose		Increase from Previous Dose
			Total mg	mg/kg[a]	
1	Cohort 1	LSF solution	1.0	0.014	
	Cohort 2	LSF solution	2.5	0.036	+ 150%
	Cohort 3	LSF solution	5.0	0.071	+ 100%
	Cohort 4	IR tablet	5.0	0.071	+ 100%
	Cohort 5	LSF solution	10.0	0.143	+ 100%
	Cohort 6	LSF solution	20.0	0.286	+ 100%
	Cohort 7	IR tablet	20.0	0.286	+ 100%
	Cohort 8	LSF solution	40.0	0.571	+ 100%
2[b]	Cohort 9	LSF solution (fed)	10.0	0.143	Not applicable
	Cohort 10	LSF solution	40.0	0.571	Not applicable

[a] Dose levels are theoretical, as calculated based on an average weight of 70kg.

[b] Part 2 (Cohorts 9 and 10) are considered exploratory

4. Selection of Subjects

The following eligibility criteria were designed to select healthy male subjects aged 18 to 55, selected from the panel of volunteers recruited by HMR, for whom the protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Eligibility criteria may not be waived by the Investigator. Any questions regarding a subject's eligibility should be discussed with the Sponsor's Medical Expert prior to subject's enrolment.

4.1. Inclusion Criteria

Subjects must meet **all** of the following inclusion criteria to be eligible for enrolment into the study:

1. Male, Caucasian volunteers, deemed healthy on the basis of a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine. Optionally, after further evaluation during the study, at the sponsor's discretion other ethnic groups may be recruited.
2. Aged 18 to 55 years.
3. With a body mass index (BMI; Quetelet index) in the range of 18 to 30.1 kg/m^2 at screening.

$$\text{Body Mass Index} = \frac{\text{weight [kg]}}{(\text{height [m]})^2}$$

4. Sufficient intelligence to understand the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial.
5. Willingness to give written consent to participate, after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or his delegate
6. Willingness to give written consent to have data entered into The Overvolunteering Prevention System

4.2. Exclusion Criteria

The presence of any of the following will exclude a subject from study enrolment:

1. Participation in another clinical trial within 3 months prior and during the study, or 5-times the half-life of the drug tested in the previous clinical trial, whichever is longer (time calculated relative to the last dose in the previous clinical trial)
2. Clinically relevant abnormal medical history, concurrent medical condition, acute or chronic illness or history of chronic illness sufficient to invalidate the subject's participation in the trial or make it unnecessarily hazardous.
3. Surgery (eg stomach bypass) or medical condition that might affect absorption of study drug taken orally.
4. Presence of abnormal physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the subject.

5. Relevant pathological abnormalities in the ECG such as a second or third-degree AV block, prolongation of the QRS complex over 120 msec or of the QTc-interval over 450 msec (QTcB or QTcF)
6. Blood pressure and heart rate in supine position at the screening examination outside one (or more) of the ranges:
    - 90–140 mm Hg systolic
    - 60–90 mm Hg diastolic
    - heart rate 40-100 beats/min

    Subjects with vital signs outside the reference range for the population being studied may be included, at the investigator's discretion, if it is unlikely to introduce additional risk factors and will not interfere with study procedures.
7. History of relevant diseases of vital organs, of the central nervous system or other organs
8. Subjects with a medical or psychiatric disorder, condition or history of such that would increase the risk associated with study participation, or impair the subject's ability to participate or complete this study, in the opinion of the investigator or the sponsor
9. Subjects with a history of severe allergies, non-allergic drug reactions, severe adverse reaction to any drug, or multiple drug allergies
10. Subjects with a hypersensitivity to the investigational drug, the control agent and/ or to inactive constituents
11. Positive tests for hepatitis B & C, HIV
12. Subjects testing positive in the drug screening
13. Presence or history of drug or alcohol abuse during the last 10 years, or intake of more than 21 units of alcohol weekly.
14. Regular daily consumption of more than one liter of xanthine-containing beverages
15. Regular daily consumption of more than 5 cigarettes daily, or use more than 3 grams (1/8 ounce) of tobacco
16. Use of a prescription medicine during the 28 days before the first dose of trial medication or use of an over-the-counter medicine, with the exception of acetaminophen (paracetamol), during the 7 days before the first dose of trial medication
17. Use of dietary supplements or herbal remedies (such as St John's Wort) known to interfere with the CYP3A4 and/or P-gp metabolic pathways during the 28 days before the first dose of trial medication (see list in Study Procedures Manual)
18. Excluded therapies which may impact on the interpretation of study results in the opinion of the investigator or sponsor
19. Febrile illness within 1 week before the start of the study
20. Objection by General Practitioner (GP) to subject entering trial.
21. Loss of more than 400 mL of blood within the previous 3 months

22. History of residing for 6 or more continuous months within the last 3 years, in regions with endemic parasitic infections as determined by the investigator
23. Possibility that subject will not cooperate with the requirements of the protocol

Part 2, Cohort 10:

The following exclusion criteria are applicable only to those subjects:

24. No contact lenses wear within 1 month prior to first dose of IMP. Contact lenses wear is not permitted during the study
25. Any ocular disorder for which topical ocular therapy is currently or chronically prescribed, including inflammatory eye disease (dry eye allergic conjunctivitis [seasonal allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis], uveitis and glaucoma)
26. Past history of ocular disease requiring ongoing treatment
27. Past ocular surgery including laser or other refractive corneal surgery
28. Evidence of eye irritation, visual difficulties, corneal opacity, ocular surface (corneal or conjunctival damage, with or without ocular symptoms)
29. Evidence of narrow anterior chamber angles causing increased risk of acute glaucoma
30. Evidence of ocular media opacity including lens opacity/vitreous opacities
31. Evidence of retinal or optic nerve pathology
32. Evidence of pronounced colour blindness, as indicated by an Ishihara score of 9/13 or below [13]

4.3. Dietary and Lifestyle Guidelines

Subjects will abide by HMR house rules during the in-house period.

No food or drink containing grapefruit will be allowed from 7 days before dosing until after the Follow-Up Visit.

No alcoholic or caffeinated drinks or smoking, will be allowed during the period from 24 h before admission until the end of each in-house period and for 24 h before each other visit. Subjects must not drink more than 3 units of alcohol daily at all other times during the study.

In fasted cohorts, during the in-house period, subjects will fast (no food or drink other than water) overnight :

- At least 9h before –24h on Day -1 until at least –20h on Day –1.
- At least 9h before dosing, until at least 4h after dosing.

When emodepside is given in the fed state (Part 2, Cohort 9), during the in-house period, subjects fast (no food or drink other than water) overnight:

- At least 10h before –24h on Day -1 until 30 min before -24 h on Day –1. At 30 min before –24h on Day –1, subjects will have a standard FDA high-calorie, high-fat breakfast consisting of: 2 fried eggs, 2 strips of bacon, 2 slices of toast and butter, 4 ounces of hash brown potatoes, and a glass of whole milk – they must finish it within 20 min.

- From the time that they finish their breakfast on Day –1, until at least –20h on Day –1.

- At least 10h before dosing, until 30 min before dosing. At 30 min before dosing, subjects will have a standard FDA high-calorie, high-fat breakfast, the contents of which will be the same as on Day –1 – they must finish it within 20 min.

- From the time that they finish their breakfast on Day 1, until at least 4 h after dosing.

- Subjects will take their dose of emodepside or placebo with 240 mL water. Water will otherwise be restricted from 1 h before until 1 h after dosing.[8,11]

Standard meals (in addition to the FDA breakfasts where applicable) will be provided at usual times, other than when subjects are fasting. However on Day −1 and Day 0:meals must be given at the same time on both days

- meals must be given after any study procedures scheduled around that timepoint).

Meal guidelines, including standard times, will be detailed in the Study Procedures Manual. Subjects will be allowed to drink water *ad libitum* at all times during the study, other than during any periods specified in Section 7. No strenuous exercise will be allowed from screening until after the Follow-up Visit.

Subjects must not expose themselves to sunlight (eg go out of doors) for longer than 15 minutes without using a strong sunblock (sun protection factor (SPF) 30 or above), or use a sunbed, or expose themselves to other sources of UV light, while they are taking emodepside and until 3 days after their last dose.

According to HMR standard procedures, and MHRA request, during the study and until 90 days following dosing, subjects must not have sex without using a condom, unless they have had a vasectomy or their partner is not of childbearing potential.

Part 2, Cohort 10

Subjects will be informed that they will need to bring their distance glasses (if applicable) to ophthalmology assessment visits. Also, their near vision will be blurred for approximately 2 hours (due to the use of mydriatic eye drops) following the eye-testing procedures at Screening Visit 2. Therefore subjects will not be able to drive or operate machinery afterwards for at least 2 hours. On Profile-Day (Day 0), the ophthalmology assessments will be repeated post-dose, but without the use of mydriatic eye drops.

5. Schedule of Events

Table 3. Schedule of Events (Part 1, Cohorts 1-8, and Part 2, Cohort 9)

Study Procedure	Screen		In-Patient Phase[a]																												See Table 4[b]				Follow-Up
	Visit		Pre-Day										Profile-Day												Evaluation											
Day ± allowable deviation	-28 to -2	-2	-1										0												1		2	3	4	5	6	7					7 +3
Subject information and Informed Consent	X																																		
Medical history (including demographics and previous / concomitant medications)	X																																		
Physical examination[c]	X																																		X
Neurological examination[d]	X																																		X
Ward Admission (approx.16h)		X																																	
Urine drugs of abuse and alcohol breath test	X	X																																	
Hours [a] (pre/post drug)		**-36**	**-24***	**-23.5**	**-23**	**-22.5**	**-22**	**-21**	**-20**	**-18**	**-16**	**-12**	**0***	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**					
Glucose, Insulin, Glucagon, and Cortisol profiles			X		X		X		X			X	X		X		X			X				X	X										
Samples for Prolactin & Leptin			X										X												X										
Administration of emodepside[e]													X																						
12-lead safety ECG[f]	X		X[f]	X	X	X	X	X	X		X	X	X[f]	X	X	X	X		X	X			X	X	X		X	X	X	X	X	X			X
ECGs extracted from continuous recordings[g]													X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]										
Vital signs[h]	X		X[h]	X	X	X	X[h]	X	X[h]	X	X	X[h]	X[h]	X	X	X	X[h]		X	X[h]		X	X	X[h]	X[h]	X	X	X	X	X	X	X				X
Adverse event monitoring[i]	X	X	X				X		X			X	X		X		X		X	X		X	X	X	X	X	X	X	X	X	X				X
PK and metabolites[j] in plasma													X[j]	X	X[j]	X	X[j]	X	X	X[j]		X	X[j]	X[j]	X[j]	X	X[j]	X	X	X	X	X				X
PK in urine[k]													0–4[k]							4–8[k]			8–12[k]	12–24[k]											
Laboratory Safety[l,m]	X[m]		X										X												X		X	X	X	X	X	X				X
Neurological[d] examination and short physical examination[c]			X[c]				X		X			X	X				X			X				X	X	X									

*: In fasted subjects, all assessments at Hour –24 on Day –1 and Hour 0 on Day 0 are immediately before the administration of study drug (emodepside). In fed subjects, all assessments at Hour –24 on Day –1 and at Hour 0 on Day 0 are before the FDA breakfast. The only exception is the 12-lead ECG continuous recording (see footnote g).

[a]: Including a 10-minute supine phase before supine BP, HR, body temperature, ECG; and for 5 minutes after each nominal timepoint for ECGs extracted from continuous recording (see footnote); and also recommended before drawing blood samples. Before sitting BP assessments minimum 3-minute sitting period.

[b]: If mean half-life of emodepside in any cohort is longer than predicted, there are options to extend in-house period, or out-patient ambulatory visits up to Day 14 if necessary, from Cohort 5 onwards and in subsequent cohorts. Refer to Option 1, Option 2, and Option 3 as outlined in Table 4.

[c]: Height at screening only, for calculation of BMI. Weight at screening for calculation of BMI, also at -24h (Day -1) for PK calculations.

[d]: Neurological examination designed for the study, see Section 8.19.4 and Study Procedures Manual

[e]: Administration of study drug while fasting or after a high-calorie, high-fat breakfast

[f]: To include 3 repeat ECGs at these timepoints, with a time difference of about 1 minute, and single recordings at other timepoints

[g]: For selected cohorts in Part 1 (see Section 8.19.2 continuous 12-lead ECG recording will be started 1 hour before dosing and continue for 24 hours post-dosing. ECGs will be extracted at predose, at three timepoints (-60, -45, and -30 minutes for fasted subjects or -90, -75, and -60 minutes for fed subjects) and at the timepoints at which PK blood samples are drawn. Subjects will be supine for 10 minutes prior to and 5 minutes after each nominal timepoint. When ECG extraction coincide with safety ECGs, vital signs and blood draws, procedures will be performed in said order.

[h]: Vital signs to include BP (supine; plus sitting BP at the indicated timepoints[‘h’]) and HR. Oral temperature only at screening and -24h.

[i]: Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety, however at these indicated timepoints will be specific questioning about AEs.

[j]: In addition to the PK sample, metabolite samples are collected only for the indicated time points [‘j’]. As an option, at the sponsor’s discretion, an additional sample of no more than 1mL may be taken at each PK timepoint from all subjects in up to 2 cohorts.

[k]: Start and end of urine collection for each bottle are indicated as hours post drug..

[l]: Hematology, Coagulation, Chemistry; Urinalysis by dip stick.

[m]: At Screening only: HIV 1, 2, Hepatitis B, C, HbA1C, in additional to hematology, coagulation, urinalysis, and chemistry.

Table 4. Follow-Up after Day 7 – Schedule Options 1, 2, or 3 Depending on Emodepside Plasma Concentrations at Day 7 in Previous Cohort(s) (from Cohort 5 onwards), Respectively.

For Screening and Days -2 through Day 8 see Table 3

OPTION 1	**Out-Patient Phase**					
Day						**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Discharge on Day 7					
Physical Examination						(see Table 3)
Neurological Examination						(see Table 3)
12-lead ECG						(see Table 3)
Vital signs[h]						(see Table 3)
Adverse event monitoring[i]						(see Table 3)
PK in plasma						(see Table 3)
Laboratory Safety[l,m]						(see Table 3)
OPTION 2	**Out-Patient Phase**					
Day	**Up to 4 visits during the period from Day 8–21 inclusive (as needed)**					**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Ambulatory Evaluation Visits, Scheduled As Needed					
Physical Examination						(see Table 3)
Neurological Examination						(see Table 3)
12-lead ECG						(see Table 3)
Vital signs[h]						(see Table 3)
Adverse event monitoring[i]	X		X	X	X	(see Table 3)
PK in plasma	X		X	X	X	(see Table 3)
Laboratory Safety[l,m]	X		X	X	X	(see Table 3)
OPTION 3	**Discharge from Ward on Day X**					
Day	**8 (±1)** (as needed)		**10 (±1)** (as needed)	**12 (±2)** (as needed)	**14 (±2)** (max.)	**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Prolonged In-House Evaluation Phase with Discharge from Ward on Day X (8-14)					
Physical Examination						(see Table 3)
Neurological Examination						(see Table 3)
12-lead ECG						(see Table 3)
Vital signs[h]						(see Table 3)
Adverse event monitoring[i]	X		X	X	X	(see Table 3)
PK in plasma	X		X	X	X	(see Table 3)
Laboratory Safety[l,m]	X		X	X	X	(see Table 3)

Table 5. Schedule of Events (Part 2, Cohort 10)

Study Procedure	Screening Visits			In-Patient Phase[a]																												Out-patient phase			Follow-Up
	1	2		Pre-Day										Profile-Day											Evaluation										
Day ± allowable deviation	-28 to -2	-7 to –1	-2	-1										0											1		2	3	4	5	6	7	10 ±1	14 ±2	18 ±2	21 +3
Subject information and Informed Consent	X																																		
Medical history (including demographics, previous/concomitant medications)	X																																		
Physical examination[b]	X																																		X
Neurological examination[c]	X																																		X
Colour blindness test[d]	X																																		
Ophthalmology exam[e]		X																																	
Ward Admission (approx.16h)			X																																
Urine drugs of abuse and alcohol breath test	X		X																																
Hours[a] (pre/post drug)			**-36**	**-24***	**-23.5**	**-23**	**-22.5**	**-22**	**-21**	**-20**	**-18**	**-16**	**-12**	**0***	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**			
Glucose and Insulin profiles				X		X							X	X		X								X	X										
Administration of emodepside[f]														X																					
12-lead safety ECG	X			X[g]		X							X	X[g]		X								X	X		X	X	X	X	X	X			X
Vital signs[h]	X			X	X	X						X	X	X	X	X							X	X	X	X	X	X	X	X	X	X			X
Adverse event monitoring[i]	X		X	X				X		X			X	X		X		X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK in plasma[j]														X	X	X				(X)			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Safety[k,l]	X[l]			X										X											X		X	X	X	X	X	X	X	X	X	X
Neurological[c] examination and short physical examination[b]				X[b]		X							X	X		X								X	X	X	X									
Travel and stay at ophthalmology clinic																	X	X	X	X	X	X														
Ophthalmology exam[m]																	X																			

* All assessments at Hour 0 on Day 0 are immediately before the administration of study drug (emodepside), and assessments at Hour –24 on Day –1 will be time-matched to Profile Day (dosing Day)

[a] Including a 10-minute supine phase before supine BP, HR, body temperature, ECG; and also recommended before drawing blood samples.

[b] Height at screening only, for calculation of BMI. Weight at screening for calculation of BMI, also at -24h (Day -1) for PK calculations.

[c] Neurological examination designed for the study, see Section 8.19.4 and Study Procedures Manual.

[d] Colour blindness to be determined at Screening visit 1.

[e] If subjects are eligible for study entry based on Screening visit 1 assessments, they will be asked to undergo an ophthalmology exam (Screening visit 2) within a week before Profile Day or on Pre–Day at the latest. All assessments for Screening Visit 1 will be performed prior to Screening Visit 2, but visits can be combined if necessary.

[f] Administration of study drug is in the fasted-state only.

[g] To include 3 repeat ECGs at these timepoints, with a time difference of about 1 minute, and single recordings at other timepoints.

[h] Vital signs to include supine BP and HR. Oral temperature only at screening and -24h.

[i] Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety, however at these indicated timepoints will be specific questioning about AEs.

[j] Timepoint shown as (X) indicates sample will be taken off-site whilst at the ophthalmology clinic. As an option, at the sponsor's discretion, an additional sample of no more than 1 mL may be taken at each PK timepoint from all subjects in up to 3 cohorts.

[k] Hematology, Coagulation, Chemistry; Urinalysis by dip stick.

[l] At Screening only: HIV 1, 2, Hepatitis B, C, HbA1C, in additional to hematology, coagulation, urinalysis, and chemistry.

[m] Ophthalmology exams will be performed on Profile-Day (Day 0) approximately 2-2.5 h post-dose. If deemed necessary by the ophthalmologist additional ophthalmology follow-up visit(s) may be scheduled for eye-related AEs.

6. Enrolment Procedures

The study will be carried-out in healthy male subjects at the following Phase 1 unit:

Hammersmith Medicines Research Limited,
Cumberland Avenue,
London, NW10 7EW, United Kingdom

The Investigator or his/her delegate should document the date when informed consent was obtained (Screening), screening dates, subject initials, Screening Number, date of eligibility and inclusion in the study (Enrolment), Subject Number (when Randomised – received treatment) or reason for not enrolling (screen failure) or not being randomized, whenever applicable.

Screening should occur between 2 and 28 days before the intended initiation of treatment: detailed procedures are described in Section 8 “Study Procedures”.

All subjects must give written consent (see Sections 8.1 and 15.1 for Informed Consent Procedures) to participate in this trial. Consent for screening evaluations may be obtained using the information and consent form for the HMR healthy volunteer panel, which was originally approved by London – Brent Research Ethics Committee (REC) and has subsequently been approved by the Phase 1 Advert Review Committee. The trial-specific information and consent form will be signed by the subject either before any screening evaluation or after the investigator confirms the eligibility of the subject for the trial and before the subject is randomized to receive the first administration of IMP. Before giving consent, subjects must read the information sheet about the trial. They must also read the consent form. They will then discuss the trial with the investigator or his deputy and be given the opportunity to ask questions. The trial-specific information sheet and the consent form must be approved by the REC. All screened subjects will be allocated a Screening Number.

After successful screening, subjects will be enrolled, and allocated to the cohort in the trial, according to their availability and the scheduled trial dates. Subjects will be assigned Subject Numbers in the order in which they are admitted to the ward, when they receive their first dose (‘Randomised’ subjects). Subject numbers for each part of the trial will be as shown in Table 6. Leading subjects in Cohort 1 will be numbered 1001 and 1002. Subject numbers will be allocated to treatments (active or placebo) according to a randomization schedule prepared by an independent HMR statistician, using a SAS program. Sufficient subjects will be screened to ensure up to 80 subjects are randomized.

As this is a First in Human study, Sentinel Dosing will be applied. In Cohort 1, the leading subjects will be randomized so that one will receive placebo and the other will receive emodepside (see also Section 7.2 for more details).

7. Study Treatments

7.1. Study Treatment Doses and Regimens

The study is divided into 2 parts; Part 1 (Cohorts 1-8) is considered the FIH, single ascending dose phase of the study, where subjects will receive a single oral fasted dose, and which includes different formulations to allow assessment of relative bioavailability. Subjects will be randomized to the following treatments:

Emodepside Liquid Service Formulation (LSF) solution (concentration of 1 mg/mL) or matching placebo solution for Cohorts 1, 2, 3, 5, 6 and 8; emodepside immediate release (IR) tablets of 5 and 20 mg or matching placebo tablets for Cohorts 4 and 7, respectively.

Part 2 is considered exploratory and will involve doses already tested. Therefore it is not considered to be FIH. The planned doses for Part 2 are 10 mg LSF solution or matching placebo solution in the fed state for Cohort 9 and 40 mg LSF solution or matching placebo solution (fasted) in Cohort 10.

The planned and actual treatments administered are described below in Table 6.

7.2. Allocation to Treatment

Randomised Subjects will be given a unique ID (subject number; Table 6) that will be recorded in the case report form (CRF), and will be retained throughout the study. This subject number will also appear on the study medication containers.

Table 6. Study Treatment: Subject Numbers, Formulation, and Dose-Levels by Cohort

Cohort	Subject Numbers[a]	Dose Level of Study Treatment	Formulation and Route of Administration	Planned Subjects	
				Emodepside	Matching Placebo
Part 1*					
Cohort 1	1001 - 1008	1.0 mg	LSF solution, p.o.	6	2
Cohort 2	2001 - 2008	2.5 mg	LSF solution, p.o.	6	2
Cohort 3	3001 - 3008	5.0 mg	LSF solution, p.o.	6	2
Cohort 4	4001 - 4008	5.0 mg	IR tablet, p.o.	6	2
Cohort 5	5001 - 5008	10.0 mg	LSF solution, p.o.	6	2
Cohort 6	6001 - 6008	20.0 mg	LSF solution, p.o.	6	2
Cohort 7	7001 - 7008	20.0 mg	IR tablet, p.o.	6	2
Cohort 8	8001 - 8008	40.0 mg	LSF solution, p.o.	6	2
Part 2**					
Cohort 9	9001 - 9008	10.0 mg	LSF solution, p.o.	6	2
Cohort 10	9501 - 9508	40.0 mg	LSF solution, p.o.	6	2

*Part 1 is the FIH, SAD part of the study.

**Part 2 is the exploratory phase (including Cohorts 9 and 10).

[a] Any subjects who are replaced in a cohort will have the subject number incremented by 100 (eg, 1001 would be replaced by 1101)

The first two subjects in Cohort 1 (subjects 1001 and 1002), will be the leading subjects. The Investigator will review all safety and tolerability data (including laboratory safety tests) up to 23 h after dosing of leading subjects before dosing the remaining subjects in the cohort.

7.3. Drug Supplies

Formulation and Supplier: Emodepside will be supplied by the Sponsor, DNDi, as emodepside LSF solution and tablets, each with matching placebo.

The study drug will be delivered by the sponsor to the study site in bulk. It will be the responsibility of a relevant member of the pharmacy/pharmacy delegate to prepare the individual treatments.

Labelling, Packaging: Emodepside supplied by the Sponsor will be manufactured, packed, labeled and shipped according to the current GMP guidelines and local legal rules. Bulk-supplies of emodepside will be delivered to the pharmacy of the Phase 1 Unit.

A relevant member of the pharmacy/pharmacy delegate will dispense study drugs as individual doses for each subject according to the Pharmacy Manual.

Preparation and Dispensing: Emodepside LSF solution and tablets will be dispensed in the Phase 1 Unit to the individual dosing containers by 2 appropriately qualified members of the pharmacy team. Instructions provided in the Pharmacy Manual/Study Procedures Manual must also be followed.

Administration: Following a fast overnight (of not less than 9 hours; fasted subjects) or an FDA breakfast (fed subjects), investigator site personnel will administer study medication to subjects on Day 0, with ambient temperature water to a total volume of approximately 240 mL.

Subjects will swallow the study medication whole, for doses of tablets, the subject will not chew the medication prior to swallowing. All subjects will be required to refrain from drinking beverages other than water during the first 4 hours after dosing. Subjects will not eat until at least 4 hours after dosing, and not until all study assessments scheduled for that time have been completed. Instructions provided in Section 4.3. and the Study Procedures Manual regarding meals must also be followed.

Compliance: Study treatment will be administered under the supervision of investigator site personnel, who will monitor the subjects according to their standard procedures to ensure treatment compliance.

7.4. Dose Escalation and Stopping Rules

During the study, the dose will be increased only if the safety and tolerability and, from Cohort 3 onwards, the PK of the previous dose is acceptable.

Planned dose levels may be changed based on emerging data. The top planned dose for the IR tablet is 20 mg and for the LSF solution is 40 mg.

The first fed dose will not exceed half the highest dose, of the same formulation, that has previously been shown to cause no safety concerns in the fasted state.

Decisions about dose escalation will be made by the participants in the Safety Review Meeting (SRG; see Section 11 on Safety Review Meetings). The dose will not be increased until the SRG have reviewed safety and tolerability data, up to a

minimum of 96 h after dosing and, from Cohort 3 onwards, a minimum of 24 h post-dose preliminary PK data from the highest dose level tested to date. The data reviewed by the SRG will be from at least 6 subjects in a Cohort (at least 4 subjects of whom have completed active treatment).

If, within a treatment group, any of the following occurs, dose escalation will be stopped:

Safety stopping criteria

- There is 1 or more serious adverse event, considered to be related to emodepside;
- 2 or more subjects who present any severe adverse event considered to be related to emodepside

If a cohort fulfils a dose escalation stopping criterion, that dose level will not be repeated.

PK stopping criteria

- predicted mean plasma concentrations in the subjects at the next scheduled dose level exceed or equal: C_{max} 634 µg/L, $AUC_{(0-24)}$ 6025 µg·h/L (based on the NOAEL level in dog toxicology studies, exposures resulting from 4 weeks of treatment at 10 mg/kg/d)

The scheduled dose of emodepside may be reduced if, for example, the results of safety tests give any cause for concern, or tolerability is poor.

If adverse events occur that cause mild or moderate discomfort but do not in any way threaten the health of the subject, that dose level may be repeated with the aim of exploring further the relationship between dose and adverse event. If, in the judgement of the SRG, it would not be reasonable to expose further subjects to the level of discomfort experienced by the subjects who have already received the dose, the next scheduled dose may be reduced. The reduction may be either to one of the dose levels that has already been given, or to an intermediate level that has not previously been given; in either case, the aim is to learn more about the relationship between adverse event and dose (or plasma concentration) of drug.

Optionally, if further information is required to guide dose escalation decisions, an independent advisor(s) may be consulted, who will have access to unblinded data (see Section 11, Safety Review Meetings).

7.5. Blinding and Procedures for Unblinding

The study drug and matching placebo will be identical in appearance in order to preserve the blind.

A sealed copy of the randomisation code will be kept in a locked file in the HMR Pharmacy. A copy will also be kept by the sponsor. The investigator will be supplied with sealed envelopes, each one containing the treatment allocation for the subject whose number appears on the outside of the envelope. Those envelopes will be kept in the trial master file, readily accessible to clinical staff. Emergency procedures for revealing medication codes are specified later in this section.

The investigators, Medical Monitor and Clinical Monitor will remain blinded until the database of finished cohorts is locked, unless safety concerns necessitate unblinding.

Sponsor staff working on the study team, staff at the investigator site(s) and the study monitor(s) will be blinded to study treatment. Optionally, a separate, unblinded monitor may be used to check drug accountability monitoring during the conduct of the study, following procedures to avoid unblinding other study personnel.

If required, as described in Section 11, advisor(s) independent from the study team may be appointed to review unblinded data to assist decision-making during Safety Review Meetings.

When a trial database has been locked, the HMR statistician will inform the sponsor of his or her intention to break the randomisation code for the finished cohorts. The statistician will break the code, and do the statistical analysis of those data.

If unblinding is required in the interest of the safety of a subject, an investigator will discuss the matter with the sponsor before opening the individual code-break envelope for that subject. In a medical emergency, the principal investigator or delegate may open the individual code-break envelope for that subject without prior consultation with the sponsor. In that event, the principal investigator or delegate will notify the sponsor as soon as possible that the randomisation code has been broken for the subject.

When the blinding code is broken, the reason will have to be fully documented and entered in source documents and the CRF.

7.6. Drug Storage and Drug Accountability

Storage: The investigational product will be stored in a secure limited access area in accordance with required storage conditions. Storage and handling instructions will be included in the Pharmacy Manual. Pharmacy staff at the clinical center will be responsible for the correct storage and handling of the study drug.

The study drug will be dispensed only under the restricted conditions defined in the present protocol and the Pharmacy Manual. Drug will be administered by the Investigator only or his/her delegate. Time of administration and initials of the person administering the drug will be documented in the CRF.

Accountability: Upon receipt of the study drugs, the Investigator or a relevant member of the pharmacy/pharmacy delegate will send to the Sponsor the corresponding acknowledgement of receipt form. This form must be duly filled (including the date of receipt) and signed by a relevant member of the pharmacy/pharmacy delegate or the Investigator. A drug movement form of all medication dispensed during the study will be maintained.

All investigational materials (medication and packaging) unused in the study will be returned to the Sponsor before or at the termination of the study, together with an accountability form documenting:

- all administered units;

- all unused treatments;
- all units returned after completion of the study, and the date of return.

7.7. Prior and Concomitant Treatments

Prior therapy as indicated in the exclusion criteria section (Section 4.2) will not be permitted. The only exception is acetaminophen (paracetamol), which may be taken up to the first dose of trial medication.

No medications (with the exception of acetaminophen (paracetamol) up to 2000mg per day), will be allowed while the subject is participating in the study except those medically indicated for the treatment of AEs. If any medication is required, the subject may be withdrawn from the study at the discretion of the Investigator and the Sponsor if use of the concomitant medication could compromise the safety of the subject or the scientific value of the trial. No dietary supplements or herbal remedies which are known to interfere with the CYP3A4 and/or P-gp metabolic pathways will be allowed while the subject is participating in the study except those medically indicated for the treatment of AEs. Use of any concomitant medication will be recorded in the source data and CRF with the following information:

- Reason for treatment;
- Name of the drug, type of formulation, and unit strength;
- Dose administered;
- Time and duration of treatment.

Medications taken within 28 days before the first dose of study medication will be documented as a prior medication. Medications taken after the first dose of study medication will be documented as concomitant medications.

8. STUDY PROCEDURES

8.1. Subject Information and Consent Form

Before any procedures are conducted, the investigator (or an appropriate delegate at the investigator site) will obtain written informed consent from each subject in accordance with the procedures described in Section 15.1 on Subject Information and Consent Form.

8.2. Screening visit 1 (all cohorts in Parts 1 and 2)

Subjects will be screened within 28 days prior to administration of the study medication to confirm that they meet the subject selection criteria for the study. Subjects who fail screening due to failure to meet inclusion and/or exclusion criteria are not permitted to be rescreened.

The following assessments will be done in order to collect historical safety data, and check inclusion and exclusion criteria.

- Inclusion/exclusion criteria review;

- Complete medical history: including demographic data, previous and concomitant medications (ie, prescription or nonprescription drugs, and dietary supplements taken within 28 days prior to the planned first dose)
- Complete Physical examination: See Section 8.19.4.
- Neurological examination: See Section 8.19.4. Also a detailed description of the neurological examination will be included in the Study Procedures Manual).
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerabilty and safety)
- Urinary drug screen (opiates, amphetamines, barbiturates, cannabis, benzodiazepines, cocaine-metabolites) and alcohol breath test;
- Serology (HIV and hepatitis);
- Body weight and height, vital signs (oral temperature, blood pressure and heart rate will be determined; Table 3);
- Colour blindness test (Ishihara score) in Part 2, Cohort 10 only.
- 12-lead ECG recording;
- Clinical safety laboratory evaluations: All biological assessments will be performed in fasting state:
    - Hematology and coagulation: hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocytes, white blood cells (WBC) with differential, red blood cells (RBC), HbA1C, activated partial thromboplastin time (aPTT), prothrombin time (PT);
    - Biochemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatinine kinase (CK), amylase, lipase, T4 (free), T3 (free), thyroid-stimulating hormone (TSH), glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium in serum;
    - Urinalysis:
        - dipstick test: glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites;

To prepare for study participation, subjects will be instructed on the use of the Dietary and Lifestyle Guidelines of the Phase 1 unit and for this study, and will be scheduled to report to the clinic for admission to the ward on Day -2.

8.3. Screening visit 2 (Part 2, Cohort 10 only)

For subjects in this exploratory cohort, in addition of differences in the timepoints the main difference compared to the other cohorts is the addition of ophthalmology assessments (see Section 8.19.5, a detailed description of the ophthalmology assessments will be added to the Study Procedures Manual. Cohort 10 procedures are described in detail in Table 5).

8.4. Admission to Ward (Day -2)

Subjects will be admitted to the ward at the Phase 1 Unit, on Day -2 approximately at 16:00 h, and a urine drug screen (opiates, amphetamines, barbiturates, cannabis, benzodiazepines, cocaine-metabolites) and an alcohol breath test will be performed.

Monitoring of AEs will be performed.

General Order for all Assessments from Day -1 through Day 7: For the study periods described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible (see also Table 3):

- 12-lead ECGs: obtain prior to vital signs and blood specimen collection, but as close as possible to scheduled time;
- Blood pressure (supine)/heart rate/oral temperature: obtain as close as possible to scheduled time, but prior to blood specimen collection;
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- For cohorts having continuous ECG reading, the minimum supine period prior to and after each nominal timepoint must be observed, and as close as possible to the blood draw for PK;
- Blood draw for PK
- Blood draw for profiles of glucose, insulin, glucagon, cortisol; single samples for prolactin and leptin (For subjects in Part 2, Cohort 10, only glucose and insulin are required, see Table 5); and laboratory safety tests (taken at the same time, if scheduled at the same timepoint);
- Blood pressure (sitting)
- PK urine specimens: collect for scheduled time frame;
- Neurological examination and short physical examination

8.5. Pre-Day (Day -1)

After their first night in the ward, subjects will be fasting overnight, fed subjects will then have a high-calorie, high-fat FDA breakfast, as described in section 4.3, and will have the following procedures completed as scheduled at various times during the day, which are all matching the schedule of procedures on the day of drug administration (Day 0, or Profile Day). The timing of all procedures must be as per the study Schedule of Events (Table 3) and Table 5 for Cohort 10:

- 12-lead ECGs: as 3-repeat readings at one timepoint, and as a single readings at the others
- Oral temperature
- Blood pressure/heart rate: in both supine and sitting position, according to the timepoints specified in the Schedule of Events. For subjects in Cohort 10, measurements are only collected in the supine position
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety):
- Blood specimens for profiles of glucose, insulin, glucagon, and cortisol; single samples for prolactin and leptin (For subjects in Part 2, Cohort 10 only glucose and insulin are required, see Table 5)
- Laboratory safety blood and urine specimens
- Neurological examinations and short physical examinations:

Subjects will receive meals at the same time points as on Profile Day, as per the Study Procedures Manual, and Section 4.3.

8.6. Profile Day (Day 0)

Part 1, Cohorts 1-8, and Part 2, Cohort 9

Subjects will be fasting overnight, as described in section 4.3, and will have the following procedures completed pre-dose (within half an hour before [Cohorts 1–8] or before the FDA breakfast [Cohort 9], except the continuous ECG monitoring – see timings below) and at the time points after administration of Study Drug outlined in (Table 3):

- In some cohorts (from Cohort 3 onwards, cohorts to be determined by the sponsor, in consultation with investigator – see Section 8.19.2), a continuous ECG recording (holter) will be started one hour prior to dosing and continue for 24 hours post-dosing.
- 12-lead ECGs: single readings, with the exception of one triplicate reading
- Blood pressure/heart rate: in both supine and sitting position according to the timepoint and specified in the Schedule of Events
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens
- PK blood specimens for metabolites
- PK urine specimen collections
- Blood specimens for profiles of glucose, insulin, glucagon, and cortisol; single samples for prolactin and leptin; Laboratory safety blood and urine specimens
- Neurological examination and short physical examination

Subjects will receive meals at the same time points as on Day -1 (as per the Study Procedures Manual and Section 4.3)

Part 2, Cohort 10

Subjects will be fasting overnight, as described in section 4.3, and will have the following procedures completed pre-dose (within half an hour before) and at the time points after administration of Study Drug outlined in Table 5.

- 12-lead ECGs: single readings, with the exception of one triplicate reading
- Blood pressure/heart rate: in the supine position
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens
- Blood specimens for profiles of glucose and insulin; Laboratory safety blood and urine specimens
- Neurological examination and short physical examination
- Ophthalmology assessments

8.7. Day 1 (24 & 36 Hours after Study Drug Administration)

Part 1, Cohorts 1-8, and Part 2, Cohort 9

Subjects will have the following procedures completed at the timepoints specified in the Schedule of Events (Table 3):

- 12-lead ECGs
- Blood pressure/heart rate: in both supine and sitting position, according to the timepoint and specified in the Schedule of Events,
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens
- PK blood specimens for metabolites
- PK urine specimen collections
- Blood specimens for profiles of glucose, insulin, glucagon, and cortisol; single samples for prolactin and leptin
- Laboratory safety blood and urine specimens
- Neurological examination and short physical examination

Subjects will receive meals at the standard time points (as per the Study Procedures Manual)

Part 2, Cohort 10

Subjects will have the following procedures completed at the timepoints specified in the Schedule of Events Table 5.

- 12-lead ECG (24h post-dose)

- Blood pressure/heart rate in the supine position (24 h and 36 h post-dose)
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety (24 h and 36 h post–dose)
- PK blood specimens (24 h and 36 h post–dose)
- Blood specimens for profiles of glucose and insulin (24h post-dose);
- Laboratory safety blood and urine specimens (24h post-dose);
- Neurological examination and short physical examination (24 h and 36 h post–dose);

8.8. Day 2 Through Day 6

Part 1, Cohorts 1-8, and Part 2, Cohort 9

Subjects will have some or all of the following procedures completed as detailed in the Schedule of Events (Table 3). Procedures must be performed at the same time each morning:

- 12-lead ECGs: as a single reading.
- Blood pressure/heart rate: in supine position
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens,
- On Day 2 only: PK blood specimens for metabolites
- Laboratory safety blood and urine specimens
- On Day 2 only: Neurological examination and short physical examination:

Subjects will receive meals at the standard time points of the ward of the Phase 1 unit (as per the Study Procedures Manual)

Part 2, Cohort 10

Subjects will undergo the same procedures and assessments as for Part 1, Cohorts 1-8, and Part 2, Cohort 9, with the exception that blood samples for PK metabolites are not required in this cohort.

8.9. Day 7 (or Day X for Option 3: Prolonged In-House Phase)

Parts 1 and 2 (all cohorts)

The following procedures will be completed in the morning on the day the subject will be discharged from the ward:

- 12-lead ECGs: as a single reading

- Blood pressure/heart rate: in supine position
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens
- Laboratory safety blood and urine specimens

If a subject experiences any AE and/or clinically significant laboratory abnormality, which is considered related to emodepside by the investigator during the 1-week in-house evaluation phase that is planned to end on Day 7, the DNDi medical monitor (or designated representative) should be notified and the subject may be asked to remain in the Phase 1 Unit until such abnormalities are deemed not clinically significant, or it is safe to discharge the subject from the ward.

In the event that results of assessments obtained after the subject's discharge from the ward indicate a significant safety concern (eg, a clinical laboratory result indicating an adverse event, or unexpectedly high levels of emodepside in plasma), a subject may be asked to return to the ward for readmission However, if a subject is unable or unwilling to remain on or return to the ward (including withdrawal of consent: Sections 8.13 and 15), and/or when outpatient follow-up is deemed appropriate, the DNDi medical monitor (or designated representative) should be so notified, and the Investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of ongoing AEs and/or abnormalities and/or clinically significant laboratory abnormality.

Subjects will be discharged on Day 7, as outlined in Figure 2 and Table 4 for Option 1.

However, as detailed in section 3.1, if in previous cohorts plasma concentrations of emodepside are still present 7 days after dosing, 2 alternative options may be employed to follow subjects after Day 7 (from Cohort 5 onwards and for all subjects in subsequent cohorts (this decision will be made during Safety Review Meeting(s) – Section 11):

Option 2: Subjects will be discharged on Day 7, as planned, as outlined in Figure 2 and Table 4 for Option 2, but will return to the clinic for ambulatory evaluation visits that will be scheduled as needed.

Option 3: Subjects will not be discharged on Day 7, as planned, but will be kept for a prolonged in-house evaluation phase of up to Day 14, as considered appropriate, before being discharged (Day X), as outlined in Figure 2 and Table 4 for Option 3.

8.10. Evaluation Visit(s) for Option 3 (Discharge from Ward) and Option 2 (Ambulatory Visit[s]Scheduled as Needed)

Option 2: Subjects (not fasting) will return to the clinic for each ambulatory evaluation visit as scheduled, to have some or all of the following procedures completed:

- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens,
- Laboratory safety blood and urine specimens,

Option 3: Subjects (not fasting) will remain on the ward for up to an additional 7 days (to Day 14). Starting from Day 8, subjects will have the following procedures every other day up to Day 12 as deemed necessary by the Investigator and Sponsor.

- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens,
- Laboratory safety blood and urine specimens

Subjects will be discharged on Day 14 at the latest or earlier if PK data from previous cohorts support a shorter in-house stay. Procedures on the day of discharge will be as described in Section 8.9. ('Day X')

Subjects in Cohort 9 will follow option 2, (up to 4 visits during the period from Day 8–21 inclusive, as needed). Subjects in Cohort 10 will return to the unit for out-patient visits on Days 10, 14 and 18, to have the following assessments:

- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety)
- PK blood specimens
- Laboratory safety blood and urine specimens

8.11. Follow-Up Visit (3 weeks [+3 Days] after dosing)

Approximately three weeks after their dose the subjects will return to the Phase 1 Unit for a Follow-Up Visit (all cohorts in Parts 1 and 2), and the following procedures will be completed:

- Complete physical examination
- Complete neurological examination
- 12-lead ECGs, as a single reading,
- Blood pressure/heart rate: in supine position,
- AE monitoring (spontaneous and solicited adverse event monitoring will include specific questioning for tolerability and safety), including any concomitant medications (ie, prescription or nonprescription drugs, and dietary supplements) taken during the duration of this study up to the follow-up visit,
- Laboratory safety blood and urine specimens
- PK blood specimens

For Cohort 10 only: If deemed necessary by the ophthalmologist additional ophthalmology follow-up visit(s) may be scheduled to characterize and assess any eye-related AEs.

8.12. Sampling time points and additional tests

With the sponsor's approval, additional time points may be introduced, and changes to time points may be made, if there is reason to believe that the change might improve the quality of the data (for example, if it is believed that an important effect of the IMP is occurring at a time when no measurements are scheduled), or if extra procedures are needed in the interest of subject safety. However, the total volume of blood taken in the trial will not exceed the value given in Section 8.18, unless in the opinion of the Investigator, it's in the subject's best interest that extra blood is taken for additional safety tests. Any additional urine collections may include continuous, total collections, if necessary. An additional 48 hours' residence in the ward and additional outpatient visits, will be permitted, in the event of a technical failure, and/or if extra observations or samples of blood or urine are needed. Similarly, the interval between outpatient visits (Option 2 only, see Section 8.10) may be changed if data collected during the study support the change.

In the case of any samples for pharmacokinetic analysis, the following will **not** be regarded as protocol deviations:

1. deviations of not more than 5 min on measurements scheduled up to and including 4 h after dosing;
2. deviations of not more than 15 min on measurements scheduled from after 4 h to 24 h after dosing;
3. deviations of not more than 1 h on measurements scheduled more than 24 h after dosing; and
4. deviations of not more than 1 or 2 days on measurements scheduled for ambulatory visits in Option 2. Deviations are shown in the schedule of events in Table 4.

For all other procedures, the following will **not** be regarded as protocol deviations:

Table 7. Permitted deviation windows for all other procedures[1]		
TIME POINT		**DEVIATION WINDOW IN RELATION TO THE SCHEDULED TIME POINT**
Day –1	**Day 0**	
Pre –24 h	Pre-dose (0 h)	Within 75 min before[2]
–24 h to –23.5 h	Up to and including 30 min after dosing	+/– 5 min[2]
After –23.5 h to –20 h	After 30 min to 4 h after dosing[5]	+/– 10 min[2,3]
After -20 h to -12 h	After 4 h to 24 h after dosing	+/– 15 min[2]
NA	more than 24 h after dosing	+/– 1 hour
NA	Ambulatory visits in Option 2	1 or 2 days[4]

1. Urine collection for laboratory safety tests will be within 2 h of the scheduled time point and all pre-dose urine samples will be collected pre-dose.
2. On Day –1 and Day 0, for the neurological and brief physical examinations, and seated vital signs assessments, the window will be extended by 5 minutes beyond those specified in the table.
3. For the cohorts that have PK urine collection, the window will be extended to +/- 15 min for the 4 h post dose neurological and brief physical examinations.
4. Deviations are shown in the schedule of events in Table 4.
5. For subjects in Cohort 10, ophthalmology tests may be done within 1.5 to 5 h following dosing.

8.13. Subject Withdrawal (see also Section 9.5)

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

If the subject withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data, with the exception of safety data, which should be collected if possible and in accordance with patient subject consent. The sponsor may retain and continue to use any data collected before such withdrawal of consent. However if the subject consents to follow-up but asks the investigator to destroy all identifiable samples taken from the subject and/or not enter into the CRF results of the follow-up examinations, the investigator will comply with the subject's requests.

If a subject withdraws from the study, the reason must be noted in the source documents and on the CRF. If a subject is withdrawn from the study because of a treatment limiting adverse event, thorough efforts should be made to clearly document the outcome of AE.

The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

It may be appropriate for the subject to return to the clinic for final safety assessments which may include all assessments normally scheduled for the study Follow-Up Visit (see Schedule of Events, Table 3).

Subjects who withdraw, or are withdrawn from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

For any subject who meets any of the following criteria, the subject may be withdrawn from the trial (ie, have no further study assessments; and no dosing will occur if this has not already taken place). Note that all adverse events must nevertheless be reported and followed-up as per Adverse Event Reporting Section 9 (unless the subject withdraws consent for further assessments).

- ALT ≥ 5 x ULN.
- ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN or international normalised ratio (INR) > 1.5 x ULN. (If a subject meets that withdrawal criterion, serum bilirubin fractionation should be performed.)
- ALT ≥ 3 x ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia). Subjects who have ALT ≥ 3 x ULN and < 5 x ULN, and total bilirubin , 2 x ULN, who do not exhibit hepatitis symptoms or rash, can continue in the study as long as they can be monitored until Follow-Up visit, or for the duration of follow-up as specified in Adverse Event Follow-Up Section 9, whichever applies.

Furthermore, the investigator may withdraw a subject for the following reasons:

- adverse events that are considered by the investigator to be related to trial medication and meet one of the following 2 criteria:
    - serious or severe; or
    - otherwise clinically significant, such as signs of allergic reaction or important bleeding events
- clinically significant intercurrent illness which could compromise the safety of the subject or the scientific value of the trial
- need for, or use of, contraindicated medication which could compromise the safety of the subject or the scientific value of the trial

- withdrawal of consent
- significant non-compliance of the subject with the requirements of the trial

If a subject is withdrawn, the investigator will make all necessary arrangements to ensure that the subject receives the appropriate treatment for the relevant medical condition.

8.14. Study Assessments

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventative actions which s/he has taken to ensure that required processes are adhered to as soon as possible. The Sponsor study team must be informed of these incidents in a timely manner. Allowable deviations for study assessments are detailed in Section 8.12 of this protocol.

To minimise variability, throughout the study, study staff should ensure:

- a minimum 10-minute supine period before the following assessments: supine BP, HR, oral temperature, ECG; and is also recommended before drawing blood samples
- a minimum 10-minute supine period prior to, and 5 minutes after each nominal timepoint for the continuous ECG reading
- a minimum 3-minute sitting period before sitting BP assessments

Throughout the study, AEs and concomitant medication will be documented as they are reported by the subjects. Subjects will also be questioned about AEs at the times that blood samples are taken, at follow-up, and at the specific timepoints detailed in the Schedule of Events (Table 3).

8.15. Assessment of Efficacy

Not applicable

8.16. PK Assessments

Blood samples for the determination of emodepside concentration in plasma will be collected at the time points indicated in the Schedule of Assessments in Table 3. The exact date and time of PK blood sampling will be recorded in the CRF.

Blood samples for PK purpose will be taken from either arm. Samples for measuring emodepside plasma concentration, and samples for measuring metabolites of emodepside will be collected either by cannulation or by venipuncture. After processing, samples will be frozen and transported on dry ice to the Bioanalysis Laboratory. Detailed instructions for collection, processing, storage, and transport of samples will be provided in the Study Procedures Manual.

Plasma will be analyzed for emodepside using a validated assay method. Full details of the method will be presented in a separate document and all the results will be reported in the bioanalytical report at the end of the study.

On Profile Day, blood samples will be collected for PK estimation and emodepside plasma concentrations. Overall, a total of 20-24 blood samples will be collected for PK purpose (plus an additional 8 samples for metabolites).

On each treatment period, the following PK parameters of emodepside will be derived for each subject:

λ_z The terminal rate constant will be estimated by log-linear regression analysis on data points visually assessed to be on the terminal log-linear phase.

$t_{1/2}$ The terminal half-life will be calculated according to the following equation: $t_{1/2} = \ln 2/\lambda_z$.

AUC_t The area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration will be calculated using a trapezoidal method.

$AUC_{t,norm}$ The area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration corrected by dose and body weight

AUC_∞ The area under the plasma drug concentration *vs*. time curve from time zero to infinity. The percentage of extrapolation of AUC_∞ should normally not exceed 20%.

AUC_∞/D The area under the plasma drug concentration *vs*. time curve from time zero to infinity, corrected for dose.

$AUC_{\infty,norm}$ The area under the concentration-time curve from time zero to infinity corrected by dose and body weight

C_{max} The observed maximum plasma concentration measured in a subject after dosing identified by inspection of the drug concentration *vs.* time data.

C_{max}/D The observed maximum plasma concentration measured in a subject after dosing identified by inspection of the drug concentration *vs.* time data, corrected for dose.

$C_{max,norm}$ The observed maximum plasma concentration corrected by dose and body weight

T_{max} The time at which C_{max} was apparent, identified by inspection of the drug concentration *vs.* time data.

MRT The mean residence time will be calculated using:

$$MRT = \frac{AUMC}{AUC_\infty}$$

Where AUMC is the area under the first moment of the concentration-time curve from zero time (pre-dose) extrapolated to infinite time.

CL/F Apparent total clearance from plasma will be calculated using the following formula:

$$CL/F = \frac{Dose}{AUC_{\infty}}$$

V_z/F Apparent volume of distribution will be calculated using the following formula:

$$V_z/F = \frac{Dose}{\lambda_z \bullet AUC_{\infty}}$$

As an option, at the sponsor's discretion, an additional sample of no more than 1mL may be taken at all PK time points, from all subjects in up to 3 cohorts. These samples may be used for future metabolite identification and/or further evaluation of the bioanalytical method. They will be stored and analysed, if required, at a laboratory designated by the Sponsor. These data will be used for internal exploratory purposes and will not be included in the clinical report.

8.17. Pharmacodynamic Assessments

Blood samples for the determination of levels of glucose, insulin, glucagon and cortisol, plus prolactin and leptin will be collected from each subject during the study, at the time points indicated in the Schedule of Assessments in Table 3 (for Part 1, Cohorts 1-8 and Part 2, Cohort 9), and Table 5 (Part 2, Cohort 10).

The exact date and time of sampling will be recorded in the CRF. Blood volumes for those samples are shown in Table 8.

Collection of samples for pharmacodynamic assessments: Blood for glucose insulin, cortisol, prolactin and leptin will be collected in tubes with a gelatin plug. Blood for glucagon will be collected in aprotinin EDTA tubes. Samples will then be transferred to the laboratory.

Processing and analysis of samples for laboratory safety tests: Processing of samples will be done by the HMR Analytical Laboratory in accordance with the laboratory's standard operating procedures.

The HMR Analytical Laboratory will do safety tests on blood and urine samples using instruments interfaced to a validated laboratory information management system (LIMS). Data from analysers that are not interfaced will be entered manually into the LIMS.

8.18. Collection Method and Total Volume of Blood

Blood collection: Blood samples for pharmacokinetic, pharmacodynamic and laboratory safety samples will be drawn either via venipuncture or using a cannula. When using a cannula: after each blood sample, the cannula will be flushed with 3 to 5 mL normal saline, to keep it patent. In order to minimise dilution of each subsequent blood sample with normal saline, the following procedure will be used: about 1 mL will be drawn via the cannula into the sampling syringe, and discarded. The definitive blood sample will then be taken.

The blood volume planned to be collected from each subject during the course of this study is detailed in Table 8. Additional samples may be required in the event of adverse events.

Table 8 Blood Volumes: Part 1 (Cohorts 1-8) and Part 2 (Cohort 9)

Options for Follow-Up	**Option 1**	**Option 2**	**Option 3**		**Option 1**	**Option 2**	**Option 3**
Test	**Number of tests**			**Blood volume (mL)**	**Total planned blood volume (mL)**		
Haematology	11	15	15	2.00	22.00	30.00	30.00
HbA1C	1	1	1	2.00	2.00	2.00	2.00
Biochemistry including free T3 and T4	11	15	15	5.00	55.00	75.00	75.00
Coagulation	11	15	15	3.00	33.00	45.00	45.00
Serology	1	1	1	2.50	2.50	2.50	2.50
Glucose*	8	12	12	2.50	20.00	30.00	30.00
Insulin, cortisol, (prolactin**	8	8	8	2.50	20.00	20.00	20.00
Glucagon	11	11	11	2.00	22.00	22.00	22.00
Leptin	3	3	3	2.50	7.50	7.50	7.50
Emodepside PK	20	24	24	5.00	100.00	120.00	120.00
Samples for metabolites	8	8	8	5.00	40.00	40.00	40.00
Discard (when blood is taken via a cannula)	17	17	17	1.00	17.00	17.00	17.00
optional samples ***	20	24	24	1.00	20.00	24.00	24.00
				Total (mL)	**361.00**	**435.00**	**435.00**

*Glucose included in biochemistry panel on Days -1, 0 (0-h timepoint) and 1
**Prolactin only to be measured on Days -1, 0 (0-h timepoint) and 1; Insulin, cortisol and prolactin to be included in the biochemistry panel on Days -1, 0 and 1
***optional samples taken from up to 3 cohorts, to cover a whole PK profile. To be retained for possible future metabolite identification/bioanalytical method development

The total volume of blood taken from each subject in the trial will be about 361 mL (or 435 mL if Option 2 or Option 3 for follow-up is required).

Additional blood may need to be collected for assay of emodepside, its metabolites, or for laboratory safety tests. No more than an extra 80 mL blood will be taken.

Subjects in Cohort 10 will provide less blood due to the fewer assessments required. The approximate total per subject in Cohort 10 will be about 286 mL. The blood volume to be collected is shown in Table 9. Additional samples may be required in the event of adverse events.

Table 9 Blood Volumes (Part 2, Cohort 10)

Test	Number of tests	Blood volume (mL)	Total planned blood volume (mL)
Haematology	14	2.00	28.00
HbA1C	1	2.00	2.00
Biochemistry including free T3 and T4	14	5.00	70.00
Coagulation	14	3.00	42.00
Serology	1	2.50	2.50
Glucose*	4	2.50	10.00
Insulin*	4	2.50	10.00
Emodepside PK	19	5.00	95.00
Discard (when blood is taken via a cannula)	7	1.00	7.00
optional samples**	19	1.00	19.00
		Total (mL)	**285.50**

*Glucose and insulin included in biochemistry panel on Days -1, 0 (0-h timepoint) and 1
**optional samples taken from up to 3 cohorts, to cover a whole PK profile. To be retained for possible future metabolite identification/bioanalytical method development

After collection, samples (blood and urine) may be stored for up to approximately 12 months after end of study before being destroyed, with the exception of the limited number of optional samples retained for possible future metabolite identification/bioanalytical method development. If those samples are required, they may be retained for up to 15 years after end of study. No samples must be destroyed without prior approval of the Sponsor.

8.19. Assessments of Safety

General questioning about AE will be done at screening (for AE onset after ICF signature), daily during the in-patient phase, at each visit, and at the Follow-Up Visit (see Section for AE recording and reporting).

8.19.1. 12-lead Safety ECG Recording

Standard 12-lead ECGs will be recorded as per Schedule of Events in Table 3 (Part 1, Cohorts 1-8, and Part 2, Cohort 9) and Table 5 (Part 2, Cohort 10). Most will be

single readings, but where triplicate ECGs are specified, 3 repeat ECGs, with a time difference of about 1 minute between them will be captured. Instructions for recording and handling of the ECGs will be included in the Study Procedures Manual.

A 3-repeat or single 12-lead ECG will be obtained on all subjects as specified in Table 3.

8.19.2. Extracted 12-lead ECG for Central Evaluation

Emodepside's effect on the placebo-corrected, change-from-predose baseline QTcF interval will be evaluated using a linear exposure response model. Cohorts in Part 1 only (from Cohort 3 onwards) will be selected for continuous monitoring by the sponsor in consultation with the investigator, based on predicted exposure to emodepside. It is currently planned that the selected cohorts will include all those dosed with the IR tablet, but cohorts dosed with LSF solution may also be included. Subjects in these cohorts will have continuous 12-lead digital ECG recording on the profile day (Day 0), starting from 1 hour before dosing, until 24 hours after dosing. Instructions for placing the recording equipment will be included in the Study Procedures Manual.

Depending on the exposure achieved, 12-lead ECGs will be extracted in up to 10 replicates from predose and post-dosing timepoints as shown in the Schedule of Events for central evaluation of potential effects on ECG parameters (heart rate, PR, QRS and QTcF). ECGs to be used in the analyses will be selected by pre-determined time points as defined in the Schedule of Events, and will be read centrally by a specialised centre.

8.19.3. Vital Signs

Blood pressure (supine and at some time points, sitting), and heart rate will be measured at times specified in Table 3 (for Part 1, Cohorts 1-8 and Part 2, Cohort 9). Only supine measurements are required for subjects in Part 2, Cohort 10 (Table 5). Oral temperature will be measured only at screening and on Day -1. Additional collection times, or changes to collection times of blood pressure, heart rate and oral temperature will be permitted, as necessary, to ensure appropriate collection of safety data.

Blood pressure and heart rate will be measured using oscillometric equipment.

Seated blood pressure: measurements will be measured using oscillometric equipment. For each specified timepoint, two measurements 2 minutes apart will be taken.

Oral temperature will be measured using disposable thermometers.

Repeat vital signs measurements

During the trial, vital signs will be repeated if they fall outside the following ranges:

Supine systolic BP:	85–160 mm Hg	Supine diastolic BP:	40–90 mm Hg
Supine heart rate:	35–100 beats/min	Oral temperature:	35.5–37.8°C

If the result of the repeat measurement is still out of range, the investigator will decide on an appropriate course of action.

8.19.4. Neurological and Physical Examination

Physical examination: will be done by a physician. The following will be examined: general appearance; head, ears, eyes, nose and throat; thyroid; lymph nodes; back and neck; heart; chest; lungs; abdomen; skin; and extremities; and the following systems will be assessed: musculoskeletal and neurological. Weight will also be measured (only at screening, and on Day -1). At certain timepoints, as detailed in Table 3, a short physical examination will be performed.

Neurological examination: will be done by a physician, and will include the following: alertness, speech, language, and comprehension; cranial nerves; motor exam; coordination/cerebellar function; tremor of the hands, legs and head (postural, kinetic and rest tremor); sensation; gait and postural stability (Pull test); mood; and sleepiness. (Full details of the neurological exam will be in the Study Procedures Manual).

8.19.5. Ophthalmology testing (Part 2, Cohort 10 only)

In Cohort 10 only, subjects will undergo the following tests at a separate baseline screening visit (Screening Visit 2; within 1 week before dosing) and on Profile–Day (Day 0) approximately 2.5-3 h after dosing.

Subjects will attend a specialist eye hospital for ophthalmology assessments to be performed by a Consultant Ophthalmologist (as shown below, and further described in the Study Procedures Manual).

- Visual symptoms
- Past ocular history
- Auto-refraction
- Best corrected distance Visual Acuity
- Colour vision assessment
- Amsler Grid assessment
- Visual field to confrontation assessment
- Ocular alignment and ocular motility assessment

- Slit lamp examination (anterior segment)
- Intraocular pressure measurement (Goldmann Tonometry)
- Post mydriatic ocular media (at Screening Visit 2 only) and retinal examination with slit lamp and lens
- Optical Coherence scanning of optic nerve and macula

Subjects will be informed that they will need to bring their distance glasses (if applicable, and their near vision will be blurred for approximately 2 hours (due to the use of mydriatic eye drops) following the eye-testing procedures at Screening Visit 2. Eye drops will not be used on the Profile-Day, so that any potential visual AEs are not obscured by the use of agents known to cause blurred vision.

8.19.6. Laboratory Safety Assessments

Blood volumes for these samples are shown in Table 8 (Part 1, Cohorts 1-8 and Part 2, Cohort 9) and Table 5 (Part 2, Cohort 10).

Collection of samples for laboratory safety tests: Blood will be taken for haematology (EDTA), and biochemistry and serology (tubes with a gelatin plug). Blood will be taken for coagulation (in sodium citrate). Urine will be collected in Universal containers. Samples will then be transferred to the laboratory.

Processing and analysis of samples for laboratory safety tests: Processing of samples will be done by the HMR Analytical Laboratory in accordance with the laboratory's standard operating procedures.

The HMR Analytical Laboratory will do safety tests on blood and urine samples using instruments interfaced to a validated laboratory information management system (LIMS). Data from analysers that are not interfaced will be entered manually into the LIMS.

9. Adverse Event Definition and Reporting

9.1. Definitions of Adverse Events

Adverse event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with that treatment. It can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Furthermore the definition of an AE includes worsening (in severity and frequency) of pre-existing conditions ("Medical history") before first Investigational Medicinal Product (IMP) administration and abnormalities of procedures (ie,, ECG, X-ray, etc.) or laboratory results which are assessed as "clinically significant". Information on AEs must be evaluated by a physician. Each AE is to be classified by the Investigator as

serious or non-serious. This classification will determine the reporting procedure for the event.

Adverse drug reaction

All untoward and unintended responses to an investigational medicinal product related to any dose administered.

Note that, according to the ICH Guideline for Good Clinical Practice (ICH GCP), a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, ie a relationship cannot be ruled out.

Unexpected adverse drug reaction

An adverse reaction, the nature, severity or outcome of which is not consistent with the applicable product safety reference information (eg Investigator's Brochure for an unauthorised investigational product, or summary of product characteristics for an authorised product).

Serious adverse event or serious adverse drug reaction

An adverse event or adverse drug reaction that is:

- fatal;
- life-threatening;
- requires or prolongs inpatient treatment;
- results in persistent or significant disability or incapacity; or
- is a congenital anomaly or birth defect;
- Any suspected transmission via a medicinal product of an infectious agent;
- An important medical event: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events/reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above.

Note: the term 'life-threatening' in the definition of 'serious' refers to an event or reaction in which the patient was at risk of death at the time of the event; it does not refer to an event or reaction which hypothetically might have caused death had it been more severe.

9.2. Procedures for Recording Adverse Events

Subjects will be carefully monitored for all adverse events, which must be recorded in source documents and clinical trial AE CRF. The investigator or delegate will question the subjects about adverse events using a non-leading question, such as 'How are you feeling?'. The investigator will also record adverse events reported spontaneously by the subjects.

The investigator will use the following criteria when deciding whether to report an abnormal test result as an adverse event.

1. The test result is associated with accompanying symptoms.

2. Results of additional diagnostic tests cause concern or necessitate medical intervention.

3. As a consequence of the test result, the dose administered to the subject is changed, the subject is withdrawn, or the subject is given concomitant treatment.

4. The investigator considers the result to constitute an adverse event.

A record will be kept in source documents and the CRF of all adverse events as reported, whether believed to be related or unrelated to the investigational treatment. The record will include the following.

- Clinical symptoms: a simple, brief description.
- Date and time of onset and end of clinical symptoms.
- Frequency: constant or intermittent.
- Severity. The Investigator will use the terminology 'Mild, Moderate or Severe' to describe the maximum severity of the AE, as described below:

Mild:	The subject is aware of the event or symptom, but the event or symptom is easily tolerated (eg, no reduction in daily activities is required).
Moderate:	The subject experiences sufficient discomfort to interfere with or reduces his or her usual level of activity.
Severe:	Significant impairment of functioning: the subject is unable to carry out usual activities and/or the subject's life is at risk from the event.

It is to be noted the distinction between severity and seriousness of AEs. A severe AE is not necessarily a serious event.

- Seriousness criteria (as defined in Section 9.1)
- Causal relationship to treatment

The assessment of causal relationship of adverse events to the administration of investigational treatment is a clinical decision based on all available information at the time of the completion of the case report form.

For both serious and non-serious AEs, the Investigator is required to assess the causal relationship between the onset of AE and the investigational treatment administration, ie, to determine whether there exists at least a reasonable possibility that the investigational treatment caused or contributed to the AE.

The following categories will be used:

- *Related*

  There is at least a reasonable possibility of a causal relationship between an adverse event and an investigational medicinal product. This means that there are facts (evidence) or arguments to suggest a causal relationship.

- *Not* related

  There is no reasonable possibility of causal relationship.

- Action taken

  None, drug treatment, subject withdrawn, other (specified).

- Outcome

  Completely recovered; Recovered with sequelae; Ongoing; Death; unknown

9.3. Adverse Event Reporting Period

AEs reporting period for this trial begins upon subject enrolment in the trial (after signature of informed consent) and ends at the Follow-Up Visit.

All AEs that occur during the AE reporting period specified in the protocol must be reported to DNDi, whether or not the event is considered medication related.

In addition, any AE that occurs subsequent to the AE reporting period that the Investigator assesses as related (ie, reasonable possibility of causal relationship) to the investigational medication should also be reported as an AE.

9.4. Procedures for Dealing With Serious Adverse Events

All SAEs are to be reported **immediately (within 24 h of awareness of SAE by the Investigator)** to the Sponsor Medical Expert and Sponsor Clinical Project Manager by telephone, and also using the serious adverse event (SAE) form sent to: pharmacovigilance@dndi.org (copy to the team members indicated in the Safety Management Plan). This includes a description of the event, onset date and seriousness criteria duration, severity, causal relationship to study drug, outcome, measures taken and all other relevant clinical and laboratory data.

The initial report is to be followed by submission of additional information (follow-up SAE form) as it becomes available. Any follow-up reports should be submitted as soon as possible, and if possible within 5 working days of knowledge.

SAE should also be reported on the clinical trial AE page of CRF. It should be noted that the form for reporting of SAE (SAE form) is not the same as the AE section of the CRF. Where the same data are collected, the two forms must be completed in a consistent manner, and the same medical terminology should be used.

In the event of any SAE which, in the investigator's opinion, justifies termination or modification of the trial, dosing will be stopped and the Sponsor Medical Expert and Sponsor Clinical Project Manager will be informed immediately (within 24 h of the investigator becoming aware of the event) by telephone, and the SAE form sent to: pharmacovigilance@dndi.org (copy to the team members indicated in the Safety Management Plan.)

In addition to immediately reporting SAEs to DNDi, the investigator will notify the main Research Ethics Committee (REC) of serious adverse events that occur during this trial, if applicable, in accordance with the standard operating procedures issued by the National Research Ethics Service (NRES).

Expectedness: DNDi is responsible for determining the expectedness of the adverse event, using the reference safety information in the Investigator's Brochure. DNDi will notify the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) of all suspected unexpected serious adverse reactions (SUSARs), and will be responsible for ensuring that the main REC is notified of SUSARs, if applicable.

- SUSARs that are fatal or life-threatening must be notified to the MHRA/EMA and REC within 7 days after DNDi becomes aware of the event.

- Other SUSARs must be reported to the REC and MHRA within 15 days after DNDi becomes aware of the event.

9.5. Procedures for Handling Withdrawals due to Adverse Events

The investigator will assess the reason for study withdrawal as far as possible and will fully record the circumstances and medical details in the CRF.

Provided that subjects give written informed consent, they will undergo the standard medical examination and laboratory tests at withdrawal from the trial which they would have undergone had they continued participation in the trial (see also Sections 8.13 and 15)

9.6. Exposure in utero

Not applicable

9.7. Adverse Event Follow Up

All AEs should be followed until they are resolved or the Investigator assesses them as chronic or stable or the subject participation in the trial ends (ie, until a final report is completed for that subject, in the case of SAEs).

In addition, all SAEs and those non-serious events assessed by the Investigator as related (i.e. reasonable possibility of causal relationship) to the investigational drug must continue to be followed even after the subject participation in the trial is over. Such events should be followed until they resolve or until the Investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented in source documents and on the CRF.

10. Data Analysis and Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Each part of the study (Part 1 and Part 2) will be reported separately. The Statistical Analysis Plan for each part will be prepared before database lock for that part.

10.1. Sample Size Determination

A sample size of up to 80 subjects (ie, up to 8 per cohort, Table 2) will be considered sufficient to examine the safety and tolerability of emodepside as well as the PK after single oral administration of the investigational drug.

Assuming a screen failure rate of approximately 50%, a total of 144 subjects will need to be screened for inclusion into this study.

For evaluation, a minimum number of 6 evaluable subjects per cohort is required.

In each cohort of up to 8 subjects, 6 are randomised to emodepside and 2 are randomised to placebo.

10.2. Definition of Study Populations Included in the Analysis

The following population sets will be identified:

- Safety Population: All subjects who received at least one dose of IMP.
- PK Concentration Population: All subjects who received at least one dose of IMP and for whom a pharmacokinetic sample has been analyzed.
- PK Parameter Population: All subjects in the PK Concentration Population for whom pharmacokinetic parameters can be derived.

In all populations, treatment will be assigned based upon the treatment subjects actually received, regardless of the treatment to which they were randomized.

Final definition of the study populations will be put in the statistical analysis plan (SAP).

General considerations for data analyses: The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error),

median, minimum, and maximum. 95% confidence intervals will be presented where appropriate for data interpretation.

Categorical data will be summarised in frequency tables with n and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented to the same number of decimal places as the raw data collected on the CRF (or to 3 significant figures for derived parameters). The mean, median and percentiles (eg, Q1, and Q3) will be presented to one additional decimal place. The standard deviation and standard error will be presented to 2 additional decimal places.

In each part of the study, placebo subjects will be pooled across cohorts taking into account formulation and fed/fasted status.

Out-of-range laboratory tests may be repeated. If a test is out of-range at baseline and repeated before dosing, the latest repeat value before dosing will be used as baseline. However, if a test is out-of-range and repeated at any other time during the study, the out-of-range value (not the repeat value) will be included in statistical summaries.

10.3. Subject Disposition

The disposition of all subjects in the safety population will be summarized including: number of subjects randomized; number completing the study, by treatment; and number discontinued from the study. The number of subject in each analysis population will be summarized by treatment

All subjects who withdraw or are withdrawn from the study will be listed, by treatment, with the reason for withdrawal.

10.4. Efficacy Analysis

Not Applicable

10.5. Analysis of Human Pharmacokinetics of Emodepside

PK concentration data will be summarised using the PK Concentration population. PK parameters will be summarised using the PK Parameter population.

For log-transformed parameters, the primary measure of central tendency will be the geometric mean; for untransformed parameters, it will be the arithmetic mean or median.[14]

For all variables, N (number of subjects in receiving the treatment/formulation in the population), n (number of observations), arithmetic mean, median, minimum, maximum, SD, %CV, and the 95% confidence interval of the arithmetic mean will be derived. For log transformed variables, all of the above plus the geometric mean, its 95% confidence interval, and the SD of the log-transformed variables, will be provided.

Plasma concentrations and PK parameters of emodepside and metabolites will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically.

The average relative bioavailability (F_{rel}) of the IR tablet will be calculated using both of the following:

$$F_{rel} = \frac{GeometricMeanAUC_{\infty, IR}}{GeometricMeanAUC_{\infty, sol}}$$

$$F_{rel} = \frac{GeometricMeanAUC_{0-24, IR}}{GeometricMeanAUC_{0-24, sol}}$$

To assess the effect of food, analysis of variance (ANOVA) models will be fitted to the fed (Part 2, Cohort 9) and relevant fasted (Part 1, Cohort 5) data with the logarithm of the pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ as the dependent variable, and fed/fasted as a fixed effect. The estimated least square means and residual variance from the model will be used to construct 90% CIs for the difference in means on the log scale for the comparison of fed versus fasted.

Concentrations of emodepside and possibly its metabolites in urine will be determined, and the amount of emodepside excreted in the urine will be estimated.

10.6. Pharmacodynamic Analysis

Pharmacodynamic variables at each planned assessment, and change in pharmacodynamic variables from baseline at each planned post baseline assessment, will be summarised by actual treatment.

10.7. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (eg physical examination, vital signs, weight and ECGs) will be summarised.

Subjects who take concomitant medication will be listed.

10.8. Safety Analysis

Safety and tolerability data will be summarized using the following parameters:

- Vital signs;
- 12-lead ECG;
- Hematology;
- Clinical chemistry;
- Urinalysis;
- Physical and neurological examination;
- AEs.
- Ophthalmology assessments (Part 2, Cohort 10)

No formal hypothesis testing of these parameters will be carried out.

10.8.1. Vital Signs and 12-Lead ECG Safety Parameters

Vital signs at each planned assessment, and change in vital signs from baseline at each planned post baseline assessment will be summarised by actual treatment.

Vital signs of potential clinical importance will be listed separately.

QT interval will be corrected using Bazett's (QTcB) and Fridericia's (QTcF) formulae. Triplicate ECG measurements will be made at some timepoints on Day -1 and Day 0, the mean of the three measurements for each subject will be used at each timepoint.

ECG variables will be summarised by treatment and time point. Differences from baseline will be summarised by treatment and time point.

QTcB or QTcF > 450 msec and increases in QTcB or QTcF from baseline of > 30 msec will be considered to be potentially clinically important. The number of subjects with a potentially clinically important QTcB or QTcF will be summarised by actual treatment and time point, giving the numbers of subjects with QTcB or QTcF > 450 msec, > 480 msec and > 500 msec, and the numbers of subjects with increases in QTcB or QTcF from baseline of > 30 msec and >60 msec.[7] A supporting listing of all subjects with an ECG value of potential clinical importance, and a separate listing of ECG findings classified as abnormal by the investigator, will also be provided.

10.8.2. Extracted 12-lead ECG for Central Evaluation

When PK data is available for the cohorts who had continuous ECG recording, the sponsor in consultation with the investigator, will assess whether emodepside exposure has been sufficient to warrant analysis of the 12-lead ECG continuous monitoring data. Any such analysis will be carried out by iCardiac Ltd (or an alternative provider).

At each protocol-specified timepoint, 10 ECG replicates will be extracted from a 5 minute “ECG window” (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position). High-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. The final QC assessment is performed by a cardiologist. The median QT, QTc, and RR value from each extracted replicate is calculated, and then the mean of all available medians from a nominal timepoint is used as the subject’s reportable value at that timepoint.

Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each timepoint. In addition to the T-wave categorical analysis, the presence of abnormal U-waves is noted.

10.8.3. Hematology and Clinical Chemistry Parameters

Data from haematology and clinical chemistry will be summarised by treatment.

Any laboratory value outside the reference interval for that variable will be flagged with an ‘H’ if it is higher than the reference interval, and with an ‘L’ if it is lower. Additionally, if, during the course of the trial, a variable changes from baseline by more than a predetermined amount (as defined by the Principal Investigator), that value will receive a flag ‘I’ if increased, or ‘D’ if decreased. Therefore, if a value both falls outside the reference interval and alters from the baseline value by more than the predetermined amount, it will attract a double flag and will be considered to be potentially clinically important.

All laboratory values of potential clinical importance will be listed. In a separate listing, laboratory values of potential clinical importance will be listed with all related laboratory results (ie haematology or clinical chemistry). Frequencies of laboratory values of potential clinical importance will be summarised.

10.8.4. Urinalysis Parameters

These parameters will be individually listed and summarized.

10.8.5. Physical and Neurological Examination

An individual data listing of abnormal physical and neurological examination findings will be provided.

10.8.6. Adverse Events

Throughout the study, all AEs observed by either medical staff or professional collaborators, or reported by the subject spontaneously or in response to a direct non-leading question, will be evaluated by the Investigator and noted in the AE section of the CRF, as described in Section 9.

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) current at the time of database lock.

All adverse events will be listed.

An AE will be considered as treatment emergent if it appeared after the first dosing, or if appeared before dosing and worsened after dosing. In case of missing onset date of AE or missing onset time of AE when it appeared the first dosing day, the AE will be considered as treatment emergent (TEAE).

The number of subjects with at least one TEAE will be tabulated by actual treatment and MedDRA system organ class and preferred term.

For each of the following, the number of subjects for which adverse events occurred will be displayed in summary tables by actual treatment as follows:

- TEAEs, by system organ class and preferred term
- drug-related TEAEs, by system organ class and preferred term

Subjects with more than one TEAE will be counted only once, at the highest severity or causal relationship, for each system organ class and preferred term. Adverse events with missing severity and/or causality will be treated as severe and related, respectively.

Adverse events leading to withdrawal, deaths and serious adverse events will be listed separately (fatal events will be listed separately from non-fatal events).

11. Safety Review Meetings

Safety will be reviewed throughout the study in Safety Review Meetings. Participants in the Safety Review Meeting ('the Safety Review Group') will be at a minimum the Principal Investigator or his/her deputy and at least one Sponsor's representative (medically qualified). As an option, independent advisor(s) will be appointed, who will have access to unblinded data to advise if required (eg, on dose escalation decisions).

The data from the first two subjects dosed in Cohort 1 (Sentinel Dosing) will be reviewed by the Sponsor and Investigator before dosing the remaining subjects in the cohort (see Section 7.2).

12. Quality Assurance and Quality Control Procedures

12.1. Investigator's File

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigator's Site File, subject clinical source documents and screening / enrolment logs. The Investigator's Site File will contain the protocol/protocol amendments, CRF and query forms, IEC and regulatory approval with correspondence, sample informed consent, drug accountability records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc. The Investigator is responsible for storing the Investigator's Site File and other study documentation in a secure location.

12.2. Case Report Forms (CRFs)

Data will be collected by authorized staff at the clinical site. It will be supervised by the investigator and signed by the investigator or by an authorized staff member. After informed consent, data for all screened subjects will be recorded in either the panel screening case report form (CRF) or the screening section of the study-specific CRF and additional source documents. The CRF is the source document for the majority of recorded data. Source documents other than the CRF will be predefined in the Source Data Agreement.

For subjects who are subsequently randomized, study-specific information will be entered into the CRF. All CRF data should be anonymized, ie, identified by study subject number only.

The investigator at each trial site should ensure the accuracy, completeness, legibility, and timeliness of all data reported to the sponsor in the CRFs and any other additional information that is required. The investigator is responsible for keeping all consent forms, screening forms, CRF and the completed subject identification code list in a secure location.

Data from subjects who are screening failures, or from enrolled subjects who leave the study before randomization will be recorded in the CRF but not entered in to the Database.

12.3. Source Documents

Before the start of the study, the sponsor and investigator will sign an agreement listing the source documents to be used in this trial. The verification of the CRF data must be by direct inspection of source documents. Source documents include subject physician's and nurse's notes, appointment book, original laboratory reports, ECG, pathology and special assessment reports, signed informed consent forms, consultant letters, General Practitioner, pharmacy records, and subject screening and enrolment logs.

The investigator must maintain source documents for possible review and/or audit by DNDi and/or Regulatory Authorities. The Investigator / designee will record the date of each subject's visit together with a summary of their status and progress in the study.

12.4. Record Retention

The investigator must keep all study documents on file for at least 15 years, or as it may be required by the applicable laws, regulations and guidelines, after completion or discontinuation of the study. After that period of time the documents may be destroyed with prior permission from DNDi, subject to local regulations.

Storage conditions must be secure, and adequate to protect study records from damage or deterioration due extremes of temperature, humidity, vermin, or any other environmental factors.

Should the investigator wish to assign the study records to another party or move them to another location, DNDi must be notified in advance.

12.5. Monitoring

Monitoring visits to the trial site will be made periodically by DNDi representatives or designated clinical monitors to ensure that GCPs and all aspects of the protocol are followed. Source documents will be reviewed for verification of consistency with data on CRFs. The investigator will ensure direct access to source documents for DNDi or designated representatives. It is important that the investigators and their relevant personnel are available during the monitoring visits.

The investigators will permit representatives of DNDi and/or designated clinical monitors to review all CRFs, medical records, laboratory work sheets and to assess the status of drug storage, dispensing and retrieval at any time during the study. The corresponding source documents for each subject will be made available provided that subject confidentiality is maintained in accord with local regulations. The reviews are for the purpose of verifying the adherence to the protocol and to ensure the study is conducted according to GCP. It is important that the investigators and other trial site staff are available at these visits.

The monitoring visits provide DNDi with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, resolve any inconsistencies in the study records, as well as to ensure that all protocol requirements, applicable regulations, and investigator's obligations are being fulfilled. Visits will take place before the study, during the study, and at study end, and will be detailed in the Monitoring Plan. Visits may also be performed by regulatory authorities.

It will be the clinical monitor's responsibility to inspect the CRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.6. Audits and Inspections

The trial site may also be subject to quality assurance audits by DNDi or designated representatives and/or to inspection by regulatory authorities or Independent Ethics Committees (IEC).

The investigators will permit representatives of DNDi and/or designated clinical monitors to inspect all CRFs, medical records, laboratory work sheets and to assess the status of drug storage, dispensing and retrieval at any time during the study. The corresponding source documents for each subject will be made available provided that subject confidentiality is maintained in accordance with local regulations.

It is important that the investigators and their relevant personnel are available for possible audits or inspections.

12.7. Data Management

Only data from Randomised subjects will be entered in to the database.

The data will be securely stored within HMR.

Data will be double-entered into a clinical database management system (ClinPlus). Edit checks and generation of queries will be done in ClinPlus. Tabulations and listings will be produced using validated, trial-specific SAS programs.

Data will be checked by the HMR QA Department. In addition, the HMR QA Department will audit the trial report; that audit will include checks to ensure that statistical output is correctly reproduced in the report.

12.8. Confidentiality of Trial Documents and Subjects Records

The investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs or other documents submitted to the sponsor, subjects should not be identified by their names, but exclusively by an identification code. The investigator should keep a subject enrolment list showing codes, names, and addresses. The investigator should maintain documents for submission to the sponsor's authorized representative, and subject's signed written consent forms, in strict confidence.

13. Protocol Deviations and Amendments

The Principal investigator will ensure that the study protocol is strictly adhered to throughout, and that all data are collected and recorded correctly on the CRF.

After the protocol has been approved by the main REC and the Regulatory Authority (MHRA), no changes may be made without the agreement of both the investigator and the sponsor.

The MHRA and main EC do not need to approve any substantial change to the protocol that needs to be implemented urgently to avoid an immediate hazard to trial

subjects. The sponsor will ensure that the MHRA and main REC are informed of urgent amendments in accordance with the detailed guidance to EU Directive 2001/20/EC and the standard operating procedures issued by NRES for NHS RECs.

Any substantial protocol amendment will be recorded on a written agreement which must be approved and signed by the sponsor and the Principal investigator and is to be submitted to the appropriate IEC and/or the MHRA for information and approval in accordance with local requirements. Approval by the RECand/or MHRA must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial [eg, change in clinical monitor[s], change of telephone number[s].

The protocol amendment can be initiated by either sponsor or by the Principal investigator.

The investigator will provide in writing the reasons for the proposed amendment and will discuss with the Sponsor's Medical Expert.

The standard text in the information and consent form template explains that the planned doses may change during the trial, and that subjects may be given any dose that has been approved by the MHRA and main REC for the trial. However, if it is considered desirable to reduce the planned dose, HMR consider it essential to fully inform the subject of the reasons, because a reduction in dose might be due to poor tolerability, and that might affect the subject's decision to remain in the trial. Wherever possible, HMR will obtain prior approval from the main REC for the information and consent form that will be given to subjects before the dose is reduced. But, owing to the nature of trials on healthy subjects, sometimes an urgent amendment to lower the planned dose will have to be implemented, to avoid immediate hazard to the subjects. In that case, subjects will be fully informed of the reason for reducing the dose, and HMR will notify the main REC and MHRA promptly of the urgent amendment, in accordance with statutory requirements.

14. Early Termination of the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, or drug safety problems.

Furthermore, both the sponsor and the investigator reserve the right to terminate the study at any time should serious or severe adverse events or any other safety issue occur during the study, prior to inclusion of the intended number of subjects, but they intend to exercise this right only for valid scientific or administrative reasons. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the subject's interest.

Reasons for early termination by the sponsor(s) may include but arenot be limited to:

- Too low enrolment rate.
- Protocol violations.
- Inaccurate or incomplete data.
- Unsafe or unethical practices.
- Questionable safety of the test article.
- Following the recommendation of the participants in the Safety Review Meetings or REC.
- Administrative decision.

Reasons for early termination by the investigator may be:

- Insufficient time or resource to conduct the study.
- Lack of eligible subjects.

In the event that a study is early terminated either by the sponsor or by the investigator, the investigator has to:

- Complete all CRFs to the greater extent possible.
- Return all test articles, CRF, and related study materials to the sponsor who provided them.
- Answer all questions of the sponsors or their representatives related to data of subjects enrolled at the site prior to study termination.
- Ensure that subjects enrolled in the study who had not yet reached a follow up time point are followed up with the necessary medical care.
- Provide in writing the reasons for his decision to the IEC and MHRA and the sponsor.

15. Ethical and regulatory requirements

The trial proposal will be reviewed by a recognised IEC, and by the MHRA. The trial will not proceed unless the sponsor obtains from the MHRA a clinical trial authorisation (CTA), and the main IEC approves the trial.

The trial will be done at HMR, in compliance with EU Directives 2001/20/EC and 2005/28/EC, The Medicines for Human Use (Clinical Trials) Regulations 2004 No. 1031 and current amendments, the Declaration of Helsinki (Brazil Revision, 2013), GMP20, the standard operating procedures issued by NRES for RECs in the UK24, and ICH Good Clinical Practice.

All subjects must give written consent to participate in this trial. Consent for screening evaluations may be obtained using the information and consent form for the HMR healthy volunteer panel, which has been approved by London – Brent Research Ethics Committee. The trial-specific information and consent form will be signed by the subject either before any screening evaluation or after the investigator confirms the eligibility of the subject for the trial and before the subject is randomized to receive the first administration of IMP. Before giving consent, subjects must read the

information sheet about the trial. They must also read the consent form. They will then discuss the trial with the investigator or his deputy and be given the opportunity to ask questions. The trial-specific information sheet and the consent form must be approved by the main REC.

Each subject is free to withdraw from the trial at any time, without giving a reason. If a subject withdraws, the investigator will ask the subject to consent to a follow-up examination. For withdrawn subjects, the investigator will use a special information and consent form which has been approved by London – Brent Research Ethics Committee and by the Phase 1 Advert Review Committee. If the subject consents to the follow-up examination but asks the investigator to destroy all identifiable samples taken from the subject and/or not enter into the CRF results of the follow-up examination, the investigator will comply with the subject's requests.

The sponsor or investigator will ensure that the MHRA and the main IEC, are informed promptly of SUSARs (see Section 9.4), and that any new reports of SUSARs from other ongoing trials of the IMPs under investigation in this trial are notified to the MHRA, and to the main IEC, if applicable. The sponsor will provide the investigator, the main IEC and the MHRA with annual safety reports of each IMP under investigation, and listings of all suspected serious adverse reaction (SSAR) reports. The sponsor will also inform the investigator promptly of any new safety or toxicology data that might affect the safety of the subjects in this study.

The investigator will promptly inform the sponsor and, if applicable, the main IEC of any serious adverse event that occurs during this trial (see Section 9.4). The investigator will provide the main IEC with annual progress reports of the trial, if the trial lasts longer than a year.

The investigator will report to the main IEC any protocol deviation that is, in his opinion, of clinical significance. The investigator will also inform the main IEC in the event of several deviations which, although of no clinical significance, cause inconvenience and/or discomfort to the subjects. The sponsor will notify the MHRA and main IEC of any serious breach of GCP (for example, the investigator puts subjects' safety at risk, falsifies data, or persistently fails to comply with this protocol or good clinical practice).

Within 90 days after the end of the trial, the sponsor will ensure that the main IEC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial.

The sponsor will supply a summary report of the clinical trial to the MHRA and main IEC within 1 year after the end of the trial.

Trial procedures at HMR will be subject to audits by the HMR QA Department, to ensure compliance with the protocol and applicable regulatory requirements.

15.1. Informed Consent Process

Inclusion in the study will occur only if the subject gives written informed consent. It is the responsibility of the investigator / designee to obtain written informed consent from each individual participating in this study, after adequate presentation of aims, methods, anticipated benefits, and potential hazards of the study. If needed, the

person will be given time to discuss the information received with members of the community or family before deciding to consent. The subject will be asked to provide written and signed consent.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

15.2. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

15.3. Compensation of volunteers

The sponsor agrees to abide by the Association of the British Pharmaceutical Industry Guidelines for medical experiments in non-patient human volunteers (2012 edition),[2] and undertakes to compensate the subjects for injuries which are considered, on the balance of probabilities, to have arisen as a result of their participation in the trial.

15.4. Insurance and Liability

The Sponsor has taken out a liability insurance as required by local regulatory requirements.

15.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, DNDi should be informed immediately.

In addition, the investigator will inform DNDi immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

DNDi is responsible for reporting any serious breaches of the protocol or of ICH GCP to the UK Regulatory Authorities.

16. Reporting and Publication of Study Results

HMR will prepare a draft Clinical Study Report for discussion with the sponsor. The report will contain results and discussion of the trial, to which will be attached a full listing of all data recorded in the CRFs, and summary tables of all important data.

Completed CRFs will be supplied separately to the sponsor by HMR.

If the data merit, DNDi encourages the communication and/or publication of the results, in accordance with the Clinical Trial Agreement for the study.

All clinical trials will be registered with a recognised clinical trial registry such as www.clinicaltrials.gov.

17. References

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