DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL

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

Short title	Safety, tolerability and PK of multiple-ascending doses of emodepside
Name of product(s)	Emodepside (BAY 44-4400)
Drug Class	Anthelmintic cyclooctadepsipeptide
Phase	1
Indication	Treatment of onchocerciasis (river blindness) and potentially other filarial diseases including lymphatic filariasis
Clinical Trial Protocol Number	DNDI-EMO-02
EudraCT	2017-003020-75
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Clinical Trial Protocol Version / Date	Version 5, 25 July 2018
Protocol Amendment Number / Date	Amendment 4

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CLINICAL TRIAL PROTOCOL SIGNATURE PAGE

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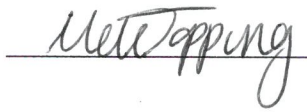
Signature  26JUL2018
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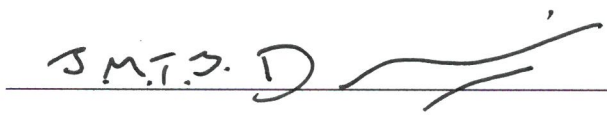
Investigator Signature  26 JUL 2018
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Investigators Signature Page

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/Research Ethics Committee (IRB/REC) 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	J.M.T.J. D	26 JUL 2018
		Date of Signature (DD/mmmYY)
Name	Jeremy Dennison	
Title	Senior Research Physician and Principal Investigator	
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Abbreviations – Glossary of terms

ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
APOC	African Program for Onchocerciasis Control
AST	Aspartate Aminotransferase
AV	Atrioventricular
AUC	Area Under the Curve
BID	Bis indie (twice-daily)
BMI	Body Mass Index
BP	Blood pressure
Bw	Body weight
^{14}C	Carbon-14
CBC	Complete Blood Count
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine Kinase
CL	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4
DALY	Disability-Adjusted Life Years
DNDi	Drugs for Neglected Diseases initiative
ECG	Electrocardiogram
EMA	European Medicines Agency
F	Female
F (parameter)	Bioavailability
FDA	Food and Drug Administration
FIH	First-In-Human
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GDRC	Generic Document Review Committee
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastro Intestinal
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

GP	General Practitioner
HDL	High Density Lipoprotein
hERG	Human ether-a-go-go-related gene
HbA1c	Glycated Haemoglobin A1c
HIV	Human Immunodeficiency Virus
HMR	Hammersmith Medicines Research
HR	Heart Rate
IR	Immediate Release
IC20	Inhibitory Concentration 20
ICF	Information Consent Form
ICH	International Conferences on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IV	Intravenous
LDH	Low Density Lipoprotein
LF	Lymphatic filariasis
LFTs	Liver function tests
LSF	Liquid Service Formulation
M	Male
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MDA	Mass Drug Administration
MedDRA	Medical Dictionary For Regulatory Activities
Mg	Milligram
MIC	Minimum Inhibitory Concentration
MIC_{100}	Minimum Concentration for 100% Inhibition
mL	Millilitre
MRT	Mean Residence Time
MTT	4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
Ng	Nanogram
OCP	Onchocerciasis Control Program
OD	Omnie die (once-daily)
OGTT	Oral Glucose Tolerance Test
PD	Pharmacodynamic
P-gp	P-glycoprotein
PI	Principal Investigator (See Note Section 13)
PK	Pharmacokinetics
p.o	Per Os (To Be Taken By Mouth)
Ppm	Parts Per Million
PR	PR Interval
PT	Prothrombin Time

PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
REC	Research Ethics Committee
QRS	QRS Interval
QTcB	Qtc Corrected By Bazett's Formula
QTcF	Qtc Correct By Fridericia's Formula
SAD	Single-Ascending Dose
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SAR	Serious Adverse Drug Reaction
SD	Standard Deviation
SOC	System Organ Class
SRG	Safety Review Group
SST	Serum-Separating Tube
SUSAR	Serious Unexpected Adverse Event
t½	Half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time Of At Which C_{max} Is Observed
TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit Of Normal
UV	Ultraviolet
Vz	Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization
WNL	Within Normal Limits

PROTOCOL SUMMARY

Trial Objectives	Primary Objective: • To investigate the safety and tolerability of emodepside (BAY44-4400) after multiple doses, administered as a Liquid Service Formulation (LSF) oral solution, in healthy male Caucasian subjects Secondary Objectives: • To investigate the pharmacokinetics (PK) of emodepside (BAY44-4400) after multiple doses, administered as an LSF oral solution. • To investigate the time-matched profiles of selected pharmacodynamics (PD) markers in plasma after multiple doses of emodepside (BAY44-4400), administered as an LSF oral solution.
Trial Endpoints	**Safety and Tolerability Variables:** • Adverse events (AEs) • Physical and neurological examination findings (including assessments of tremor of the hands and fingers, coordination/cerebellar function (finger to finger, finger to nose, with eyes open and closed), pupil size and reaction to light) • Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP) • 12-lead Electrocardiogram (ECG (including HR, PR, QRS, QTcB, QTcF)) • Clinical laboratory tests: Haematology: haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets, reticulocytes, white blood cells (WBC) including differential, red blood cells (RBC), glycated haemoglobin (HbA1C) (at screening and Day 120 only); Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT); Biochemistry: serum 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; At baseline (screening visit 1) and day 9 additional hormones: leptin and prolactin levels Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites. • Ophthalmology assessments, including visual symptoms, past ocular history, best corrected distance visual acuity, colour vision assessment, Amsler grid assessment

	Pharmacodynamic Variables: • Time-matched profiles of glucose, glucagon, insulin, and cortisol. • Oral glucose tolerance test (OGTT) **Pharmacokinetic Variables:** Emodepside plasma concentration–time data will be used to derive the following PK parameters of emodepside: • After the first dose of emodepside (Day 0): • Main PK parameters: • Cohorts 1 & 2: AUC_{24}, , AUC_{24}/D, C_{max}, C_{max}/D • Cohort 3: AUC_{12}, AUC_{12}/D, C_{max}, C_{max}/D • Exploratory PK parameters: • Cohorts 1 & 2: $AUC_{24,norm}$, $C_{max,norm}$, t_{max}, MRT_{last}, V_z/F • Cohorts 3: $AUC_{12,norm}$, $C_{max,norm}$, t_{max}, MRT_{last}, V_z/F • After multiple doses of emodepside (Day 9): • Main PK parameters: • Cohorts 1 & 2: AUC_{∞}, AUC_{∞}/D, AUC_{24}, AUC_{24}/D, $C_{max,ss}$, $C_{max,ss}/D$ • Cohort 3: AUC_{∞}, AUC_{∞}/D, AUC_{12}, AUC_{12}/D, $C_{max,ss}$, $C_{max,ss}/D$ • Exploratory PK parameters: $AUC_{\infty,norm}$, $AUC_{12,norm}$, $AUC_{24,norm}$, AUC_{last}, AUC_{last}/D, $AUC_{last,norm}$, $C_{max,ss,norm}$, $t_{1/2}$, λ_z, t_{max}, MRT_{∞}, V_z/F, CL_{ss}/F • Other optional parameters: AUC_{t-inf}, $\%AUC_{extra}$, points terminal • Accumulation ratios $RA(C_{max})$ and $RA(AUC_{tau})$ will be calculated • C_{trough} will be derived from the concentration data (Days 1–9). The above parameters may be calculated for the metabolites of emodepside, as appropriate. In urine, the amount and concentration of emodepside and its metabolites may be measured for up to 24 h on up to 4 occasions during the study. The appropriate specific PK parameters to be calculated will be decided, according to the concentration.
Trial Design	This will be a single-centre, single-blind, randomized, placebo-controlled, parallel-group, multiple-dose, dose-escalation study. The study will evaluate safety, tolerability, PK and PD of emodepside, after administration as an LSF oral solution, over 10 days, in healthy male Caucasian subjects. Treatment duration was defined based on single ascending dose PK data modelling as well as anticipated duration of treatment with emodepside for safety. The study will be performed in a single site specialized in Phase 1 studies. Each cohort will comprise 8 healthy Caucasian male subjects, 6 of whom will be allocated to receive emodepside, and 2 of whom will be allocated to receive placebo. 3 cohorts will be recruited, to test 3 multiple dose levels of

	emodepside LSF oral solution. This will be a single-blind study. The Investigator and Sponsor will remain blinded, so as not to potentially introduce bias. However, the Investigator and Sponsor may choose to review unblinded data at the Safety Review Group for a particular cohort (the process will be described in the Safety Review Group Charter). Each subject will attend a screening visit within the 4 weeks before their first dose of study medication (on Day 0). Eligible subjects will be admitted to the ward on the evening of Day –3. They will remain on the ward until the morning of day 14 (17 nights in a row), during which they'll receive once- or twice-daily oral doses of emodepside or placebo for 10 days. Safety, tolerability, PD and PK assessments will be done regularly before, during, and after dosing. Each subject will undergo a full day of assessments (excluding PK) on the day before dosing (Day –1), and a similar full day of assessments (including PK) on the first (Day 0) and last days of dosing (Day 9). In addition, they will undergo an Oral Glucose Tolerance Test (OGTT) on Day –2, Day 1, Day 8 and Day 120. Subjects will be discharged from the ward 5 days after their last dose of study medication, if the Investigator has no safety concerns. Subjects will attend the ward for out-patient visits on Days 17, 20, 23 and 27 (+/- 2 days). Subjects will attend a follow-up visit on Day 30 (+/- 2 days), and 3 long-term follow-up visits on Days 60, 90 and 120 (+/- 2 days). The end of the trial is defined as the final long-term 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 long-term follow-up visit, whichever is later.
Main Entry Criteria	**Inclusion:** 1. Male, Caucasian volunteers, deemed healthy based on a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine. 2. 18 to 45 years of age. 3. Normal body weight (BMI; Quetelet index) in the range 18 to 30.1 kg/m^2 at screening. 4. Blood pressure and heart rate in the supine position prior to randomisation must be within the ranges • 90–140 mm Hg systolic, • 60–90 mm Hg diastolic; • heart rate 45-100 beats/min. 5. 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. 6. 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. 7. Willingness to agree to the contraceptive requirements of the study from the first dose until 120 days after the last dose of study medication 8. Willingness to give written consent to have data entered into the Overvolunteering Prevention System **Exclusion:** 9. Administration of a licensed or unlicensed medicinal product as part of another clinical trial within the 3 months before, or within 5 half-lives of, their first dose of study medication, whichever is longer, or is currently in the follow-up period for any clinical trial. 10. Clinically relevant abnormal medical history, concurrent medical condition, acute or chronic illness or history of chronic illness (such as diabetes mellitus or other abnormalities of glucose homeostasis) sufficient to invalidate the subject's participation in the trial or make it unnecessarily hazardous. 11. Past surgery (eg stomach bypass) or medical condition that might affect absorption of study drug taken orally. 12. 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. 13. Loss of more than 400 mL of blood within 3 months before admission. 14. Clinically relevant history of vital organ disease or other disease of an organ or the central nervous system. 15. Current or previous medical or psychiatric disorder, condition or history of such (eg seizures) that, in the opinion of the Investigator or the Sponsor, would increase the risk associated with study participation, or impair the subject’s ability to participate or complete this study. 16. Positive test for hepatitis B, hepatitis C or HIV 17. Febrile illness within 1 week before the first dose of study medication. 18. History of severe allergy, non-allergic drug reactions, severe adverse reaction to any drug, or multiple drug allergies. 19. Subjects with hypersensitivity to any ingredient of the study medication, including the active ingredient, emodepside. 20. Presence or history of drug or alcohol abuse in the last 10 years, or intake of more than 21 units of alcohol weekly. 21. Regular daily consumption of more than one liter of xanthine-containing beverages. 22. Regular daily consumption of more than 5 cigarettes daily, or use more than 3 grams (1/8 ounce) of tobacco. 23. Use of a prescription medicine during the 28 days before the first dose of study medication or use of an over-the-counter medicine (with exception of acetaminophen (paracetamol)), during the 7 days before the first dose of study medication. 24. Use of dietary supplements or herbal remedies (such as St John’s

	Wort) that are known to be inducers or inhibitors of CYP3A4, or other co-medications known to be relevant substrates of CYP3A4, during the 28 days before the first dose of study medication (see list in the Study Procedures Manual). 25. Use of dietary supplements or herbal remedies (such as St John's Wort) that are known to be strong inhibitors of P-gp, or other co-medications known to be relevant substrates of P-gp, during the 28 days before the first dose of study medication (see list in the Study Procedures Manual). 26. Relevant pathological abnormalities in the ECG at screening, such as a second or third-degree AV block or prolongation of the QRS complex over 120 msec or QTc-interval over 450 msec (QTcB or QTcF). 27. Evidence of drug abuse (via urine testing) at the screening assessment or admission to the ward 28. Use of excluded therapies that may impact on the interpretation of study results in the opinion of the Investigator or Sponsor. 29. Objection by General Practitioner (GP) to subject entering trial. 30. 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. 31. Possibility that subject will not cooperate with the requirements of the protocol. 32. No contact lenses wear within 1 month before dosing. Contact lenses wear is not permitted during the study. 33. 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) 34. Past history of ocular disease requiring ongoing treatment 35. Past ocular surgery including laser or other refractive corneal surgery 36. Evidence of eye irritation, visual difficulties, corneal opacity, ocular surface (corneal or conjunctival damage, with or without ocular symptoms) 37. Evidence of narrow anterior chamber angles causing increased risk of acute glaucoma 38. Evidence of ocular media opacity including lens opacity/vitreous opacities 39. Evidence of retinal or optic nerve pathology 40. Evidence of pronounced colour blindness, as indicated by an Ishihara score of 9/13 or below
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, behavioural, or administrative reasons. • Subjects who withdraw, or are withdrawn from the study may be replaced

<table>
<tr><td></td><td>at the discretion of the Investigator upon consultation with the Sponsor.</td></tr>
<tr><td>Study Duration</td><td>• Each subject's participation in the study will last for up to 21 weeks, and will include a screening visit (within 4 weeks before dosing), an in-house 2-week evaluation period (Day –3 to Day 14), followed by 4 outpatient visits (on Days 17, 20, 23 and 27), a follow-up visit (on Day 30), and 3 long-term follow-up visits (on Days 60, 90 and 120).</td></tr>
<tr><td>Study treatments</td><td>Test-Drug: Emodepside LSF oral solution (1 mg/mL) or matching placebo.
Planned dose levels:
<table>
<tr><th>Cohort</th><th>Dose level</th><th>Formulation</th></tr>
<tr><td>1</td><td>5 mg, OD, for 10 days</td><td>LSF oral solution (1 mg/mL)</td></tr>
<tr><td>2</td><td>10 mg, OD, for 10 days</td><td>LSF oral solution (1 mg/mL)</td></tr>
<tr><td>3</td><td>10 mg, BID, for 10 days (single dose on Day 9)</td><td>LSF oral solution (1 mg/mL)</td></tr>
</table>
Emodepside administration will be given as fasted doses of LSF oral solution. Each morning dose will be given after an overnight fast of at least 9 h. On Days 0, 1, 8 and 9, subjects will fast until at least 4 h after dosing. On Days 2 to 7, subjects will fast until at least 1h after dosing. In Cohort 3, subjects will also fast for 2 h before and until 1 h after their evening dose.

Dose escalation will be decided by the Safety Review Group (SRG) at the Safety Review Meeting. The dose will not be escalated until the SRG have reviewed safety, tolerability and PK data until 48 h after the final dose of study medication in at least 4 subjects on active treatment (ie, at least 6 subjects overall), and agree that it is appropriate to give a higher dose; that decision will be taken in the Safety Review Meeting, before dosing of the subsequent cohort. The next planned dose level may be reduced, or a dose level may re-tested or an intermediate dose level selected, based on emerging data.

The dose level will not exceed 20 mg LSF oral solution (1 mg/mL) per day.

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

<u>Safety stopping criteria</u>
• There is 1 or more SAE, considered to be related to emodepside;
• 2 or more subjects in the same treatment group who present any severe or clinically significant AEs considered to be related to emodepside

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

<u>PK stopping criteria</u>
• predicted mean plasma concentrations in the subjects at the next scheduled dose level exceed or equal: C_{max} 612 µg/L (based on the highest dose in the Single Ascending Dose (SAD) study DNDi-EMO-001))

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.</td></tr>
</table>

	If AEs 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 AE. If, in the judgement of the Safety Review Group (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 AE and dose (or plasma concentration) of drug.
Sample Size	Up to 24 healthy male subjects (not including replacement subjects), in up to 3 cohorts, of 8 subjects.
Statistics	No formal statistical sample size estimation has been performed for this, due to the exploratory nature of this study. 6 subjects per dose level (cohort) is considered sufficient to examine the safety and tolerability of emodepside as well as the pharmacokinetics after single and multiple doses. Any withdrawn subjects will be replaced. Interim analyses will be performed. Safety: Safety and tolerability data will be summarized using the Safety Population. Safety and tolerability data will be summarized using the following parameters: • Vital signs; • 12-lead ECG; • Haematology; • Clinical chemistry; • Coagulation; • Urinalysis; • Physical and neurological examination; • Ophthalmology assessments • AEs. No formal hypothesis testing of these parameters will be carried out. **Pharmacodynamic:** PD data will be summarized using the Safety Population. PD variables at each planned assessment, and change in PD 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, Standard Deviation (SD), % Coefficient of variance (%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. Concentrations of emodepside and its metabolites in urine may be determined and the amount of emodepside excreted in the urine will be estimated, if applicable

1. Background and Study Rationale

1.1. Background information

Filarial diseases cover infectious diseases caused by parasitic nematode worms transmitted by arthropod vectors: onchocerciasis (river blindness), lymphatic filariasis (LF, or elephantiasis), and loiasis (African eye worm, or *Loa loa* filariasis).

More than 1 billion of the world's poorest people are at risk (WHO, 2015; Zouré et al, 2015).

An estimated 18 million people suffer from onchocerciasis (Vos et al, 2015), with 99% of cases in 31 African countries, and 187 million at risk in 2015 . Although the disease is almost exclusively confined to Africa, some foci still exist in Yemen and South America (Brazil and Venezuela) (OMS, 2016).

Severe visual impairment and blindness are considered the most severe complications of onchocerciasis and their control was the main objective of the initial international control program, the Onchocerciasis Control Programme (OCP) in West Africa. Onchocerciasis is still the world's second-leading infectious cause of blindness.

Onchocercal dermatitis and itching are the most common symptoms of the disease and represent a significant public health problem in affected communities. Incessant itching may cause insomnia, can affect work productivity and social relationships (Okoye & Onwulirir, 2007) and can even induce premature child weaning by affected mothers (Amazigo, 1994; Alonso et al, 2009).

The clinical manifestations of the disease have been attributed to the host immune response to dying or dead microfilariae in the skin and the eyes.

The World Health Organization (WHO) estimates[11] that 746,000 patients are visually impaired, 265,000 are blinded and more than 4 million suffer from severe itching due to onchocerciasis (Amazigo, 1994).

The burden associated with onchocerciasis is estimated at more than 1 million disability-adjusted life years (DALYs) in 2013 worldwide (Alonso et al, 2009).

Onchocerca volvulus (*O. volvulus*) is a helminth belonging to the nematode class (roundworm), causing onchocerciasis in humans. The disease is contracted through the bite of an infected female blackfly (*Simulium*), which transmits infective larvae (L3) to a person. Once it has penetrated into the host, the larvae moult twice before reaching the adult stage. The average reproductive life span of an adult female worm in the human body is estimated to be 10 years (WHO, 2010) but they can live up to 15 years. Adult worms induce the formation of subcutaneous or deeper nodules where they settle (in the former case, they seem to be particularly frequent near the joints). Adult males migrate from nodule to nodule (explaining the F:M sex ratio of 2:1 in the nodules). After mating, a female releases on average 1600 (GBD, 2015) new microfilariae (first stage larvae, L1) per day (however, in *O. volvulus*, the release of microfilariae by the female worms is not constant, with one estimate that there are, on average, 4 reproductive cycles per year).

The microfilariae migrate to the dermis where they are eventually ingested by a blackfly, in which the parasite completes its life cycle by moulting twice to become an infective larvae (L3). During a subsequent blood meal, these larvae may then be transmitted to another host to continue the cycle.

Ivermectin is the standard treatment for onchocerciasis patients. The drug kills the microfilarial stage of the parasite and provides temporary sterilization of adult female worms, preventing vector-borne transmission and re-population of the host's skin with microfilariae, but only for several months. Ivermectin relieves onchocerciasis-associated itching and reversible skin and eye clinical manifestations, preventing blindness and chronic skin lesions. However, skin microfilariae and itching may resume in some patients as soon as 3-6 months after ivermectin treatment. Therefore, the treatment must be repeated regularly for several years to control both the production of microfilariae and the clinical symptoms.

The current treatment approach is a preventative chemotherapy based on the administration of ivermectin once or twice a year to all the population in endemic areas. Widespread use was made possible with Merck's ivermectin donation (Plaiser et al, 1991) to African Control programs in 24 African countries under the direction of APOC/WHO until 2015 (Schulz-Key & Soboslay, 1994).

Control programs with ivermectin have been in place for over 20 years, resulting in an important reduction in transmission and morbidity. However, treatment must be repeated at least yearly for 10 or more years, to break the transmission cycle and reach elimination, making implementation difficult in some endemic areas. A new, longer-acting drug is therefore needed that would kill the adult worm, stop the production of new microfilariae and break the transmission of *O. volvulus*. Additionally, the programs have to be implemented with special measures in regions where onchocerciasis is co-endemic with loiasis.

Loiasis, also called "eye worm", is another filarial diseasethat occurs exclusively in West and Central Africa; an estimated 13 million people are infected with *Loa loa* (Gardon et al, 1997). Humans contract the disease through the bite of a deer fly or mango fly (*Chrysops spp*).

Serious adverse events (SAE) following the use of ivermectin in *Loa loa*-infected patients were observed in areas of high prevalence of eye worm (Meredith & Dull, 1998). The most severe complication is an encephalopathy which is triggered by the massive death of microfilariae induced by the drug, and which can be fatal or leave long-term sequelae (Fobi et al, 2015).

Loa loa infection limits the use of ivermectin in Mass Drug Administration (MDA) programs in co-endemic areas, and is an impediment to achieving WHO elimination goals for onchocerciasis. Furthermore, reports of a suboptimal response of *O. volvulus* to ivermectin may be a sign of developing resistance (Hotez & Kamath, 2009; Gardon et al, 1997).

Thus, there is an urgent need for a macrofilaricidal drug, killing or sterilizing permanently *O. volvulus* adult worms, which could be used in individual case management and, after appropriate testing, as an alternative drug to ivermectin in MDA programs.

A macrofilaricidal drug could reduce the number of MDA cycles needed, thereby easing control program implementation and enhancing chances in disease elimination, particularly in *Loa loa* co-endemic areas.

Emodepside is a promising candidate to kill the adult and sexually mature *O. volvulus* as explained below. This study investigates the safety, tolerability and pharmacokinetics of emodepside (BAY44-4400) after multiple doses, in healthy male Caucasian subjects.

1.2. Rationale for the development of emodepside

Emodepside (BAY 44-4400) is a registered drug for animal health, commercialized by Bayer AG under the name of Profender® (in combination with praziquantel) or Procox® (in combination with toltrazuril). Emodepside was shown to be macrofilaricidal against a variety of filarial nematodes as investigated in both *in vitro* and *in vivo* studies: *Achatocheilonema vitae*, *Litomosoides sigmodontis*, *Brugia malayi*, *Onchocerca gutturosa*, *Onchocerca lienalis* (Zahner et al, Int J Parasitol, 2001; Zahner et al, Acta Tropica, 2001).

The mechanism of action of emodepside is complex and not fully understood. In gastrointestinal nematodes, as well as the free-living nematode *Caenorhabditis elegans* it has been shown that emodepside interacts with the g-protein coupled receptors latrophilin LAT-1 (Wilson et al, 2003). It was indicated that this interaction is responsible for the paralytic effects on the pharynx. However, it has not been investigated whether LAT-1-like proteins are expressed in all nematodes (e.g. filariae) or if emodepside is able to modulate those. Emodepside also interacts with SLO-1, a calcium activated potassium channel, which finally results in flaccid paralysis (inhibition of locomotion, feeding, egg-laying and slowed development) (Guest et al, 2007).

Therefore, emodepside targets different life stages of the parasites, including the adult stage. This is a very important feature since treatments targeting adult worms should result in the reduction of the number of cycles required to free patients from infection and hopefully allow treatment in regions where Loa loa co-infection is present. Hence, emodepside can be considered to be a promising drug candidate able to fulfil unmet medical needs for the treatment of filarial diseases.

A first-in-human (FIH) double-blind, placebo-controlled study of single ascending doses of emodepside in healthy Caucasian men has been conducted in the UK in 10 cohorts, with data from the final 2 cohorts (Cohorts 9 and 10) currently under evaluation. However, the first 8 dose steps, single doses ranging from 1 to 40 mg, have been evaluated with respect to safety, tolerability and pharmacokinetics. The preliminary results are favourable, support continuing the Phase I development program and merit the further development of emodepside. Details of those interim results are presented in the Summary of Clinical Human Data section below. In the present repeat dose study, pharmacokinetic as well as safety and tolerability of the liquid service formulation of emodepside, given over 10 days will be tested.

1.3. Summary of non-clinical information

Summary of Pharmacology Data

A set of primary pharmacodynamic studies was performed to characterize and assess the efficacy and specificity of emodepside. *In vitro*, emodepside showed potent anthelmintic activity on microfilariae and worms. The Minimum Inhibitory Concentration (MIC_{100}) value for motility was 0.1 µM emodepside, equivalent to 111.9 ng/mL. The biological viability test (enzymatic MTT assay) also showed significant anthelmintic potency *in vitro* with a clear dose-response in *Litomosoides sigmodontis* (MIC_{100} = 10 µM). The worms were unable to recover as demonstrated in an extended 40-day *in vitro* assay. The model organisms employed ie. *Onchocerca gutturosa, Brugia pahangi, Onchocerca lienalis, Litomosoides*

sigmodontis, and *Acanthocheilonema viteae*, are considered to represent a reasonable *in vitro* disease model and predictor for efficacy against *O. volvulus* infection. *In vivo* studies in BALB/c mice and jirds, naturally infected with *Litomosoides sigmodontis,* also showed the significant potential of emodepside as a macrofilaricidal drug for human use. In these infection models, emodepside reduced peripheral microfilaremia, from 10 mg/kg onwards, in mice and jirds; even in immune compromised mice there was evidence of anthelmintic activity. Furthermore, emodepside significantly reduced the number of recovered adult worms in mice (at 1 and 12.5 mg/kg) and in jirds (at 10, 50 or 100 mg/kg). In mice, comparable macrofilaricidal potency was found at all tested doses and reduction of adult worms was approximately 80%.

In conclusion, primary *in vitro* and *in vivo* pharmacology studies showed the significant potential of emodepside as a macrofilaricidal drug for human use. This chemotherapeutic compound was active against both stages of parasites ie. microfilariae and adult filarial nematodes *in vitro* and thus, non-clinical pharmacology data of emodepside supports its use for treatment of onchocerciasis in humans.

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.

The *in vitro* hERG assay showed no critical potential for QT prolongation (IC20 19 µM). *In vitro*, emodepside weakly inhibited GABA-A receptor (46 % at 10 mmol/L). In pituitary neuroendocrine preparations, 500 nmol/L emodepside reduced GABAergic activity.

Safety pharmacology and repeated dose toxicity studies revealed the central nervous system as a target organ, with changes in behaviour, activity, tremor and gait abnormalities in rats, mice and dogs. A No Observed Adverse Effect Level (NOAEL) of 5 mg/kg. was defined in dogs and rats after repeated administration (4-week repeat oral dose toxicity study). 10 mg/kg body weight was established as the NOEL for effects on the nervous system in fasted rats after acute administration. Toxicokinetic (TK) analysis suggested an AUC of 1,611 ng.h/mL and C_{max} of 238 ng/mL after 5 mg/kg/day in dogs following 4-week exposure. In rats, an AUC of 1.9 µg.h/mL and C_{max} of 79 ng/mL was found following 4 weeks of emodepside given with food at 50 ppm, corresponding to 4.2 mg/kg in males and 5.0 mg/kg in females.

After a single oral application of emodepside to rats, no biologically relevant effect on respiratory parameters was noted (10-100 mg/kg). Also, in dogs, no effect on respiratory functions was observed at the tested doses. Hyperglycaemia was observed in rats in acute and repeated dose fed 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.

Emodepside showed no adverse effect on ECG results 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 body weight. A threshold plasma level of 0.1 µg/mL was determined for this effect. The clinical 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 body weight.

Summary of Pre-Clinical Pharmacokinetic Data

In vitro studies showed moderate plasma protein binding of emodepside in all tested species, with similar values in mice, dogs and humans (fraction unbound of 1.0−1.6 %). In rats, gerbils and rabbits the fraction unbound was slightly higher (2.7−3.1 %). The relevant Phase 1 biotransformation pathway of emodepside in humans, as well as in animal species, was 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 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 h in rats and 42 to 35 h in dogs after p.o. and i.v. administration, respectively.

Biodistribution studies with ^{14}C-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 faecal/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 most of the dose excreted into faeces. The major metabolites in faeces were identified as the hydrolysis product, its dehydrated and oxidized derivatives as well as three oxidized metabolites.

After repeated oral dosing of ^{14}C labelled emodepside in rats, the parent compound was the major component found in rat plasma with a small amount of metabolite M1 detected in rat plasma.

Toxicokinetic data were obtained from Good Laboratory Practice (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).

Summary of Toxicology Data

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, 800 ppm equals in rats approx. 77-95 mg/kg, 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 haematological parameters, triglyceride and glucose levels in the plasma and lipid and glycogen stores. These toxicological findings pointed to a diabetes-related condition (inhibition of insulin secretion followed by increased glucose levels and reduced leptin levels, as confirmed by mechanistic studies). In mice, the NOAEL after 14 weeks of treatment was 50 ppm (10.5-16.8 mg/kg). The NOAEL in the 14-week rat study was defined at 10 ppm (m: 0.73, f: 1.11 mg/kg per day); In 4-week rat studies 50 ppm (equals 4–5 mg/kg) was defined as the NOAEL.

In dogs, doses starting from 10 mg/kg per day for 4 weeks resulted in clinical signs like vomiting, tremor and unsteady gait. At 20 mg/kg, 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.

Several reproductive and developmental toxicity studies were conducted in rats and rabbits. Effects of emodepside on 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, fetotoxicity, foetal malformations and various skeletal/visceral anomalies or deviations. Clinical signs of systemic maternal toxicity were evident at dose rates ≥ 6 mg/kg. Overall, severe maternal toxicity at 18 mg/kg resulted in adverse effects on foetal development. The NOAEL for maternal toxicity in rats was 2 mg/kg and the NOAEL for developmental toxicity was 0.5 mg/kg. 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 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.

Additional endocrinology studies confirmed the involvement of emodepside in hormone deregulation (reduced estradiol [E2], triiodothyronine [T3], insulin, leptin and prolactin levels and enhanced thyroid-stimulating hormone [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.

General Pre-Clinical Summary

The non-clinical data package of emodepside is comprehensive due to the authorization of 3 veterinary medicinal products (Profender Spot-on, Profender

Tablets, Procox). The safety pharmacology studies, ADME studies, acute and repeated-dose studies, studies on reproduction and development, genotoxicity studies, local tolerance and sensitization studies, as well as mechanistic studies on the toxicological mode of action are included in the submission package. All these non-clinical studies (all pivotal studies were conducted under GLP conditions) are sufficiently to support this Phase I study in human subjects.

1.4. Summary of clinical human data

To date, a total of 79 healthy male volunteers have been exposed to the study treatment: either emodepside Liquid Service Formulation (LSF) solution or immediate release (IR) tablets (dose range 1.0–40 mg LSF solution, and doses of 5 mg and 20 mg tablets; 59 volunteers) or placebo (20 volunteers). Volunteers received the treatment in fasted conditions, or, for the 8 subjects of Cohort 9 (receiving 10 mg LSF solution or placebo), after a high-fat, high calories breakfast.

This study was divided into 2 parts: part 1 with cohorts 1 to 8 including 63 subjects (47 exposed to emodepside) and part 2 with cohorts 9 and 10 including 16 subjects (12 exposed to emodepside).

Based on preliminary data, maximum exposure was observed with the 40 mg LSF solution (Cohort 8), with a mean C_{max} of 612 ng/mL and AUC of 4,315 ng.h/mL. So far, based on unblinded safety data from Part 1 of the study, those doses have been safe and tolerance was acceptable. Based on an unblinded review of the safety data, total number of subjects with at least one Treatment Emergent Adverse Events (TEAEs) are summarised below by System Organ Class (SOC).

Based on preliminary data, across all treatments within Part 1 (Cohorts 1-8), no serious AEs were reported. Overall, 53 non-serious TEAEs were reported by 31 out of the 63 subjects (49%), of which 45 non-serious TEAEs reported by 25 out of the 47 subjects (53%) exposed to emodepside and 8 non-serious TEAEs reported by 6 out of the 16 subjects (37%) exposed to placebo. All TEAEs (related or not) were mild or moderate in severity. All the treatment-related TEAEs resolved spontaneously within less than 24 h and without treatment.

A total of 14 subjects exposed to emodepside (22.2%) experienced 20 TEAEs that were considered by the Investigator to be related to emodepside treatment. In addition 4 TEAEs, reported in 3 subjects exposed to placebo, were assessed as related to treatment. All TEAEs, whether related or not, were mild or moderate in severity. The most frequently reported TEAEs were eye disorders and nervous system disorders.

All the treatment-related TEAEs resolved spontaneously within less than 24 h and without treatment.

Table 1: Total number of subjects with at least one TEAE (unblinded Cohorts 1 to 8 – by SOC

SOC	*Placebo*		*Emodepside*									Total n=63 (%)
	LSF; n=12 (%)	tablet; n=4 (%)	0.1 mg* LSF; n=1 (%)	1 mg LSF; n=5 (%)	2.5 mg LSF; n=6 (%)	5 mg LSF; n=5 (%)	5 mg tablet; n=6 (%)	10 mg LSF; n=6 (%)	20 mg LSF; n=6 (%)	20 mg tablet; n=6 (%)	40 mg LSF; n=6 (%)	
Any TEAE	**5 (41.7)**	**1 (25)**	**1 (100.0)**	**3 (60.0)**	**0**	**3 (50.0)**	**3 (60.0)**	**5 (83.3)**	**3 (50.0)**	**2 (33.3)**	**5 (83.3)**	**31 (49.2)**
Eye disorders	0	1 (25.0)	0	0	0	0	1 (20.0)	2 (33.3)	1 (16.7)	0	5 (83.3)	**10 (15.9)**
Gastrointestinal disorders	1 (8.3)	1 (25.0)	0	0	0	1 (16.7)	0	0	0	1 (16.7)	0	**4 (6.3)**
General disorders and administration site conditions	0	0	0	0	0	2 (33.3)	0	0	0	0	0	**2 (3.2)**
Infections and infestations	0	0	1 (100.0)	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	1 (16.7)	**5 (7.9)**
Injury, poisoning and procedural complications	1 (8.3)	0	0	0	0	0	0	0	1 (16.7)	0	0	**2 (3.2)**
Musculoskeletal and connective tissue disorders	0	0	0	1 (20.0)	0	1 (16.7)	1 (20.0)	0	0	1 (16.7)	1 (16.7)	**5 (7.9)**
Nervous system disorders	2 (16.7)	0	0	2 (40.0)	0	1 (16.7)	1 (20.0)	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)	**12 919)**
Respiratory, thoracic and mediastinal disorders	1 (8.3)	0	0	0	0	0	0	1 (16.7)	1 (16.7)	1 (16.7)	0	**4 (6.3)**
Psychiatric disorders	0	0	0	0	0	0	1 (20.0)	0	0	0	0	**1 (1.6)**

*After 0.1 ml of IMP was administered, it was discovered that the subject was not eligible for the study due to an AE, and dosing was stopped

Preliminary interpretation:

Non-serious TEAEs involving Central Nervous System (CNS) disorders were reported in 10 out of 47 subjects exposed to emodepside, and included headache (n=6 subjects), dizziness (n=4) and somnolence (n=1), while 2 out of 16 subjects receiving placebo reported headache. The AEs were mild or moderate in severity and more frequent at the highest dose (40 mg). The AEs that were considered as treatment related were dizziness (n=4), headache (n=2) and somnolence (n=1), all mild in severity, reported in 7 out of 47 subjects exposed to emodepside, and headache of moderate severity, reported in 1 out of 16 subjects exposed to placebo. No abnormal findings were found on objective neurological examination.

Non-serious eye disorders AEs were reported in 9 out of 47 subjects receiving emodepside, and included: vision blurred (n=5 subjects), photophobia (n=2), visual impairment (n=2), accommodation disorder (n=1), whereas 1 out of 16 subjects

receiving placebo reported dry eye (n=1). All eye disorders AEs were of mild to moderate intensity, resolved spontaneously (without treatment), and were more frequently reported with highest dose (40 mg). Among them, the AEs of blurred vision, photophobia ("Increased ocular light sensitivity"), visual impairment ("distorted contrast perception", "distorted colour perception") reported by 8 out of 47 subjects receiving emodepside were considered as treatment-related by the Investigator. Also of note, at the highest dose (40 mg), lightheadedness (n=1), dizziness (n=1) or headache (n=1) were reported concomitantly to blurred vision.

None of the volunteers met any of the protocol-specified withdrawal criteria and overall tolerability to emodepside has been acceptable up to 20 mg. The presence of post-dose visual disturbances in subjects of Cohort 8 receiving either 40 mg solution or placebo may warrant some concern and escalation was stopped at this dose level.

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 have been roughly dose-proportional, with low to moderate inter-individual variability. The plasma half-life during the first 24 h is very short for a single dose of emodepside. After 3, 7, 16 and 47 h the maximum plasma concentration is reduced to 50%, 25%, 12.5% and 6.25% respectively. Terminal plasma half-life is 523 h. Although data of Cohort 9 (which was treated with a single dose of emodepside with food) are still under review, administration of the LSF of 10 mg with a high fat, high-calorie meal resulted in a clinically relevant food effect with a reduction of AUC to ~67%, C_{max} to 42% and a delay of the T_{max} up to 2.33 h. Therefore, the recommendation of administration of the emodepside (LSF) under fasted conditions is given.

In fasting conditions, a dose and plasma concentration-dependent decrease in insulin plasma concentration (13 pmol/L or below) after emodepside administration was reported, with a maximum between 0 and 4 h. In parallel, dose and plasma concentration-dependent increases in fasting serum glucose levels above 5.8 mmol/L were observed, with a maximum between 0 and 4 h (none of these increases were considered clinically significant by the Investigator, and therefore were not reported as AE) and a maximum of 12.7 mmol/L at 2 h at the dose of 40 mg LSF solution. In fasted conditions, both blood insulin decrease and glucose increases occurred over the 4 h after single dosing with emodepside in most cases. In Cohort 9 (6 subjects exposed to emodepside, and 2 subjects to placebo), 10 mg LSF of emodepside was given with food and a physiological increase of glucose and insulin was observed, as expected under normal conditions. A decrease in insulin due to emodepside could not be observed. This is interpreted that administration of food overrules a possible effect of emodepside on the secretion of insulin under fasted condition.

There was no report of clinically significant laboratory abnormalities, or abnormalities in vital signs, ECG parameters or physical examination throughout the study, regardless of the formulation.

Data of Cohort 10 (treated with a single 40 mg dose of emodepside and focused at ocular system assessment) are still under analysis, however no serious AEs were reported following administration of the LSF of 40 mg. 6 subjects were exposed to emodepside, and, 2 subjects to placebo. Overall in cohort 10, 22 non-serious AEs related to emodepside were reported, all mild or moderate in severity. 4 subjects reported AEs related to emodepside (eye disorders including blurred vision, photopsia, visual impairment, eye pain and reduced visual acuity), with an onset in

most cases close to T_{max} and of various durations. In addition, the following were considered related to emodepside: 2 subjects reported concomitant feeling of relaxation, 1 subject reported dizziness, 1 subject reported disturbance in attention and hypervigilance, 1 subject reported concomitant balance disorder and disorientation, and 1 subject reported oral paresthesia (of the tongue) that lasted for approximately 6 h.

1.5. Assessment and management of risk

The factors taken into account in the assessment of risk to subjects in this study are as follows:

- The planned daily doses of emodepside have been administered to humans as single doses and were well tolerated. Based on the first-in-human clinical study, overall tolerability to emodepside has been acceptable up to 20 mg. Post-dose visual disturbances were observed more frequently at 40 mg, and although these visual and nervous system disturbances were considered non-serious and mild in intensity, dose escalation was stopped at this dose level. All visual disturbances were transient in nature and resolved spontaneously within 24 h, and without treatment.
- During the study, the dose will be increased only if the PK, safety and tolerability of the previous dose is acceptable and if the investigator and sponsor's medical representative agree that it is appropriate to give a higher dose. The next planned dose level may be reduced, or a dose level may re-tested or an intermediate dose level selected, based on emerging data. The total daily dose will not exceed 20 mg emodepside (as LSF solution at a concentration of 1 mg/mL).
- Subjects will undergo a comprehensive ophthalmology assessment at screening and will be excluded from the study if any ocular pathology is detected. Additional ophthalmology assessments will be performed during the study, if clinically indicated.
- Subjects will undergo a full neurological assessment at screening, Day 0 and at discharge from the ward in order to detect and assess any neurological disorder or change.
- In the first-in-human trial (DNDI-EMO-01), emodepside was shown to undergo bi-phasic elimination with a dominant half-life ($t_{1/2\ 0\text{-}24}$) estimated at approximately 11 h, and terminal half-life ($t_{1/2\ 0\text{–}\infty}$) over 520 h. In order to comprehensively assess safety parameters over this period, volunteers will be followed up until Day 120.

2. Study Objectives and Endpoints

2.1. Objectives

2.1.1. Primary Objective

- To investigate the safety and tolerability of emodepside (BAY44-4400) after multiple doses, administered as a LSF oral solution, in healthy male

Caucasian subjects.

2.1.2. Secondary Objectives

- To investigate the pharmacokinetics (PK) of emodepside (BAY44-4400) after multiple doses, administered as an LSF oral solution.
- To investigate the time-matched profiles of selected pharmacodynamic (PD) markers in plasma, after multiple doses of emodepside (BAY44-4400), administered as an LSF oral solution.

2.2. Study Endpoints

2.2.1. Primary Safety Endpoint(s)

- Adverse events (AEs)

2.2.2. Other Safety Endpoint(s)

- Physical examination findings
- Neurological examination findings (including assessments of tremor of the hands and fingers, coordination/cerebellar function (finger to finger, finger to nose, with eyes open and closed), pupil size and reaction to light)
- Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP)
- 12-lead ECG (including heart rate (HR), PR, QRS, QTcB, QTcF)
- Clinical laboratory tests:
    - Haematology: haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets, reticulocytes, white blood cells (WBC) including differential, red blood cells (RBC), glycated haemoglobin (HbA1C; at screening and Day 120 only);
    - Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT);
    - Biochemistry: serum 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;
    - At baseline (screening visit 1) and Day 9 additional hormones: leptin and prolactin levels
    - Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites.
- Ophthalmology assessments: including visual symptoms, past ocular history, best corrected distance visual acuity, colour vision assessment, Amsler grid

assessment

2.2.3. Secondary Endpoint(s)

Pharmacokinetic Variables:

Emodepside plasma concentration–time data will be used to derive the following PK parameters of emodepside:

- After the first dose of emodepside (Day 0):
  - Main PK parameters:
  - Cohorts 1 & 2: AUC_{24}, AUC_{24}/D, C_{max}, C_{max}/D
  - Cohort 3: AUC_{12}, AUC_{12}/D, C_{max}, C_{max}/D
- After multiple doses of emodepside (Day 9):
  - Main PK parameters:
  - Cohorts 1 & 2: AUC_{∞}, AUC_{∞}/D, AUC_{24}, AUC_{24}/D, $C_{max,ss}$, $C_{max,ss}/D$
  - Cohort 3: AUC_{∞}, AUC_{∞}/D, AUC_{12}, AUC_{12}/D, $C_{max,ss}$, $C_{max,ss}/D$
- Accumulation ratios $RA(C_{max})$ and $RA(AUC_{tau})$ will be calculated
- C_{trough} will be derived from the concentration data (Days 1−9).

The above parameters may be calculated for the metabolites of emodepside, as appropriate.

Pharmacodynamic Variables:

- Time-matched profiles of glucose, glucagon, insulin, and cortisol
- Oral glucose tolerance test (OGTT)

2.3. Exploratory PK variables

Emodepside plasma concentration–time data will be used to derive the following PK parameters of emodepside:

- After a single dose of emodepside (Day 0):
  - Cohorts 1 & 2: $AUC_{24,norm}$, $C_{max,norm}$, t_{max}, MRT_{last}, V_z/F
  - Cohorts 3: $AUC_{12,norm}$, $C_{max,norm}$, t_{max}, MRT_{last}, V_z/F
- After multiple doses of emodepside (Day 9):
  - $AUC_{\infty,norm}$, $AUC_{12,norm}$, $AUC_{24,norm}$, AUC_{last}, AUC_{last}/D, $AUC_{last,norm}$, $C_{max,ss,norm}$, $t_{1/2}$, λ_z, t_{max}, MRT_{∞}, V_z/F, CL_{ss}/F
  - Other optional parameters: AUC_{t-inf}, $\%AUC_{extra}$, points terminal

3. Study design and study design rationale

3.1. Study design

This will be a single-centre, single-blind, randomized, placebo-controlled,

parallel-group, multiple-dose, dose-escalation study.

The study will evaluate the safety, tolerability, PK and PD of emodepside, after administration as an LSF oral solution, over 10 days, in healthy male Caucasian subjects. Treatment duration was defined based on single ascending dose PK data modelling as well as anticipated duration of treatment with emodepside for safety.

The study will be performed in a single site specialized in Phase 1 studies.

Each cohort will comprise 8 healthy Caucasian male subjects, 6 of whom will be randomised to receive emodepside, and 2 of whom will be randomised to receive placebo. 3 cohorts will be recruited, to test 3 multiple dose levels of emodepside LSF oral solution.

This will be a single-blind study, where the Investigator and Sponsor will remain blinded in each cohort, so as not to potentially introduce bias.

3.2. Study duration and duration of subject participation

Each subject will attend a screening visit within the 4 weeks before their first dose of study medication (on Day 0).

Eligible subjects will be admitted to the ward on the evening of Day –3. They will remain on the ward until the morning of day 14 (17 nights in a row), during which they'll receive daily oral doses of emodepside or placebo for 10 days. Subjects in Cohorts 1 and 2 will receive emodepside once-daily and those in Cohort 3 will receive emodepside twice-daily (at 12 h intervals) during that time.

Safety, tolerability, PD and PK assessments will be done regularly before, during, and after dosing. Each subject will undergo a full day of assessments (excluding PK) on the day before dosing (Day –1), and a similar full day of assessments (including PK) on the first (Day 0) and last days of dosing (Day 9). In addition, they will undergo an Oral Glucose Tolerance Test (OGTT) on Day -2, Day 1, Day 8 and Day 120.

Subjects will be discharged from the ward 5 days after their last dose of study medication (Day 14), if the Investigator has no safety concerns. Subjects will attend the ward for outpatient (ambulatory) visits on Days 17, 20, 23 and 27 (± 2 days). Subjects will attend a follow-up visit on Day 30 (± 2 days), approximately 3 weeks after their last dose of emodepside. Subjects will also have long-term follow-up visits on Days 60, 90 and 120(± 2 days).

The study Schedule of events (Section 5) provides a detailed overview of all study procedures, which are further discussed in Section 8 (Study Assessments).

3.3. Definition of the end of trial

The end of the trial is defined as the final long-term follow-up visit (Day 120 +/- 2 days) 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.

3.4. Rationale of study design

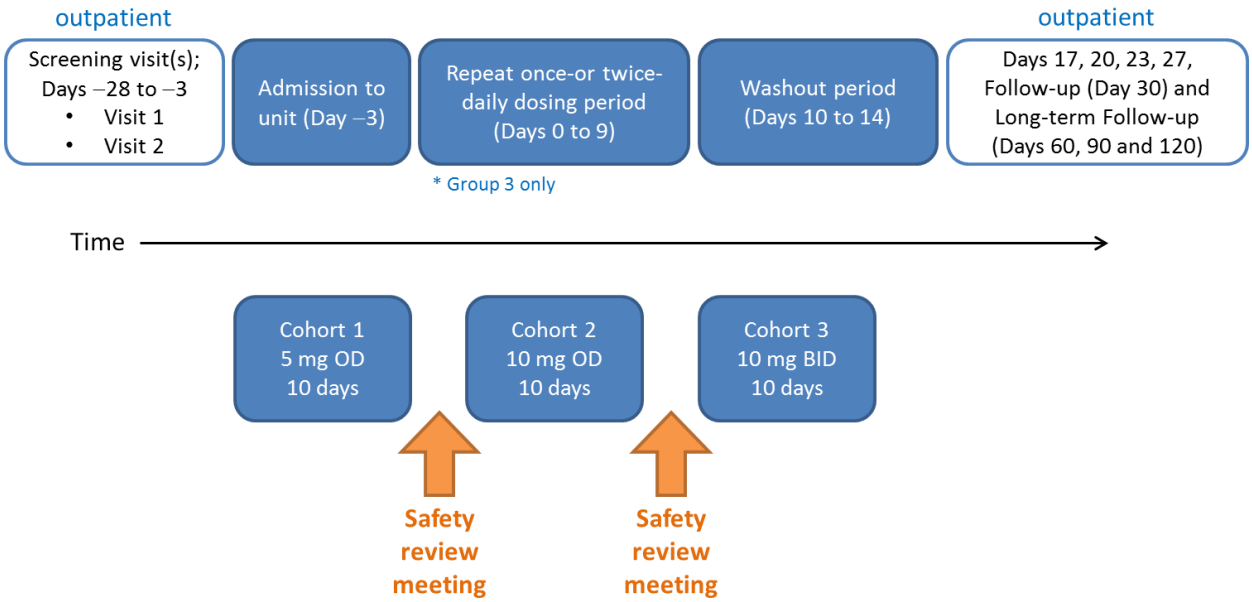
The study will be performed in healthy male Caucasian volunteers.

The study is performed in a single-blinded design, in which the subjects are blinded and will not know which treatment (active or placebo) they are given. The Investigator and Sponsor will remain blinded during each cohort, so as not to potentially introduce bias. For safety and dose escalation purposes, the data may also be unblinded at the end of each cohort, for review by the Safety Review Group (detailed in Section 7.10). Placebo has been included to assess whether any observed effects are treatment-related or simply reflect the study conditions.

Subjects will be given an extensive ophthalmological assessment at Screening Visit 2 and full neurological assessment at screening and Day 0, to ensure that they don't have any pre-existing conditions that might confound the results of post-dose assessments.

The decision about dose escalation will be taken in the Safety Review Meeting, before dosing of the subsequent cohort (see Section 11).

Figure 1- Overall study flow chart



Based on the data from the single dose-escalating FIH trial (DNDI-EMO-001), the dose level in this study will not exceed 20 mg LSF oral solution (at a concentration of 1 mg/mL) per day.

4. Selection of Subjects

The following eligibility criteria were designed to select subjects 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 DNDi Medical Monitor before 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 based on a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine.
2. 18 to 45 years of age
3. Normal body weight (Body Mass Index (BMI); Quetelet index) in the range 18.0 to 30.1 kg/m^2 at screening
4. Blood pressure and heart rate in the supine position prior to randomisation must be within the ranges
    - 90–140 mm Hg systolic,
    - 60–90 mm Hg diastolic;
    - heart rate 45-100 beats/min.
5. 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
6. 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
7. Willingness to give written consent to have data entered into The Overvolunteering Prevention System (TOPS)
8. Willingness to agree to the contraceptive requirements of the study from the first dose until 120 days after the last dose of study medication

4.2. Exclusion criteria

Any of the following will exclude a subject from study enrolment:

1. Administration of a licensed or unlicensed medicinal product as part of another clinical trial in the 3 months before the first dose of study medication, or within 5 half-lives of administration of a medicinal product given in the previous study (whichever is longer), or otherwise in the follow-up period for any clinical trial.
2. Clinically relevant abnormal medical history, concurrent medical condition, acute or chronic illness, or history of chronic illness (such as diabetes mellitus or other abnormalities of glucose homeostasis) sufficient to invalidate the subject's participation in the trial or make it unnecessarily hazardous
3. Past surgery (eg stomach bypass) or medical condition that might affect absorption of the study drug when taken orally
4. Presence of abnormal physical findings, ECG, or laboratory values at the screening assessment that could interfere with the objectives of the trial or the safety of the subject
5. Loss of more than 400 mL of blood within the 3 months before admission
6. Clinically relevant history of vital organ disease, or other organ or central nervous system disease
7. Current or previous medical or psychiatric disorder (eg seizures) that, in the opinion of the Investigator or the Sponsor, would increase the risk and ability

to participate in and/or complete the study

8. Positive test for hepatitis B, hepatitis C or HIV
9. Febrile illness (eg fever) within 1 week before the first dose of study medication
10. History of a severe allergy, non-allergic drug reaction, severe adverse reaction to any drug, or multiple drug allergies
11. Hypersensitivity to any ingredient of the study medication, including the active ingredient (emodepside)
12. Presence or history of drug or alcohol abuse in the last 10 years, or intake of more than 21 units of alcohol weekly
13. Regular daily consumption of more than one litre (L) of beverages containing xanthine
14. Daily consumption of more than 5 cigarettes or more than 3 grams (1/8 ounce) of tobacco
15. Use of a prescription medicine during the 28 days before the first dose of study medication, or use of an over-the-counter medicine (with exception of acetaminophen (paracetamol)), during the 7 days before the first dose of study medication
16. Use of dietary supplements or herbal remedies (such as St John's Wort) that are known to be inducers or inhibitors of CYP3A4, or other co-medications known to be relevant substrates of CYP3A4, during the 28 days before the first dose of study medication (see list in the Study Procedures Manual)
17. Use of dietary supplements or herbal remedies (such as St John's Wort) that are known to be strong inhibitors of P-gp, or other co-medications known to be relevant substrates of P-gp, during the 28 days before the first dose of study medication (see list in the Study Procedures Manual)
18. Relevant pathological abnormalities in the ECG at screening, such as:
    - second or third-degree atrioventricular (AV) block; or
    - prolongation of the QRS complex > 120 msec; or
    - QTc-interval (QTcB or QTcF) > 450 msec.
19. Evidence of drug abuse (via urine testing) at the screening assessment or admission to the ward
20. Use of excluded therapies that may impact on the interpretation of study results in the opinion of the Investigator or Sponsor
21. Objection by General Practitioner (GP) to subject entering trial
22. History of residing for 6 or more continuous months during 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
24. Wearing of contact lenses during the 1 month before the first dose of study medication. Contact lens wear is not permitted during the study
25. Presence of an 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. 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

4.3. Dietary and lifestyle guidance

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 including long-term follow-up visits. Subjects must not drink more than 3 units of alcohol daily at all other times during the study (1 unit = ½ pint of beer, 1 small glass of wine or 1 measure of spirits).

No strenuous exercise will be allowed from screening until after the Follow-up Visit, and from 48 h before each long-term follow-up visit.

Subjects should not expose themselves to sunlight for longer than 15 minutes without using a strong sunblock (factor (SPF) 30 or above), use a sunbed, or expose themselves to other sources of UV light (such as UV lighting in clubs), while taking the study medicine and until 3 days after their last dose

Standard meals will be provided at the usual times designated by the Investigator. Subjects will be allowed to drink water ad libitum at all times during the study.

Subjects should fast (no food or drink, except water) for 10 h before Screening Visit 1. During the in-house period (Days –3 to 14), subjects will fast on the following occasions:

- for at least 9 h overnight until the morning of Day –2, and until the OGTT has been administered;
- for at least 9 h before the morning of Day –1, and will have their first meal of the day after their morning assessments are complete.
- for at least 9 h overnight before their morning dose on Days 0–9, until 4 h after that dose on Days 0, 1, 8 and 9, and 1 h after the dose on other days;
- in Cohort 3, subjects will additionally fast for at least 2 h before and 1 h

after their evening dose on Days 0–9;

- for at least 9 h before their assessments on Day 10, 11, 12, 13, and 14, Day 23 outpatient visit, and the Follow-up (Day 30 ±2 days) and long-term follow-up visits (Day 60, 90 and 120 ±2 days).

On each occasion, subjects will be required to fast until scheduled assessments for the relevant time have been completed.

During the study (according to HMR procedures), and for 120 days after the subject's last dose of study medicine, subjects must not have sex without using a condom, unless they have had a vasectomy or their partner is not of childbearing potential.

Subject's near vision will be blurred for approximately 2 h (due to the use of mydriatic eye drops) following the eye-testing procedures at Screening Visit 2, so they should not drive or operate machinery for that time afterwards. On Day 10, the ophthalmology assessments will be repeated post-dose, but without the use of mydriatic eye drops. If subjects report visual AEs, ophthalmology assessments should be done at the ophthalmological clinic, as soon as an appointment can be scheduled.

5. Schedule of events

5.1. Table 2: Schedule of events overview

Procedure	Screening		Day (s)												Follow-up (Day 30 ±2 Days)	Long-term follow-up visits (Days 60, 90, and 120 ±2 Days)[18]
	Day –28 to –3		–3	–2	–1	0	1	2–8	9	10–14	17 (±2)	20 (±2)	23 (±2)	27 (±2)		
	Visit 1	Visit 2														
Subject demographics and informed consent	X															
Inclusion/Exclusion Criteria	X					X										
Medical history	X															
Inpatient stay			←							→						X
Outpatient visit	X	X									X	X	X	X	X	X
Drugs of abuse screen and alcohol breath test[1]	X		X													X
Full physical examination[2]	X							X		X					X	
Short physical examination[2]					X	X	X	X	X	X	X	X	X	X		X
Full neurological examination[3]	X					X				X						
Short neurological examination[4]					X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmological examination[5]	X	X								X						
Oral Glucose Tolerance Test (OGTT)[6]				X			X	X								X
Glucose, insulin, glucagon and cortisol[7]					X	X	X		X	X					X	
Administration of emodepside[8]						X	X	X	X							
12-lead safety ECGs[9]	X				X	X	X	X	X	X					X	

Procedure	Screening		Day (s)												Follow-up (Day 30 ±2 Days)	Long-term follow-up visits (Days 60, 90, and 120 ±2 Days)[18]
	Day –28 to –3		–3	–2	–1	0	1	2–8	9	10–14	17 (±2)	20 (±2)	23 (±2)	27 (±2)		
	Visit 1	Visit 2														
Vital signs[10]	X				X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring[11]	⟷															
PK of emodepside in plasma[12]						X	X	X	X	X	X	X	X	X	X	
PK of metabolites of emodepside in plasma[13]						X			X							
PK of emodepside and metabolites in urine[14]						X			X							
Laboratory safety tests[15]	X				X	X	X	X	X	X			X		X	X
Serology[16]	X															
Leptin and prolactin[7,17]	X								X							

1. Alcohol breath tests and drugs of abuse screen will be performed at Screening Visit 1 and Day–3. At long-term follow-up visits (Days 60, 90 and 120), only alcohol breath tests will be performed.
2. A full physical examination will be done at Screening Visit 1 and Follow-up and before the morning dose on Days 3–8 inclusive, and on Day 14. To include height at Screening Visit 1 and weight at Screening Visit 1 and on the morning of Day –1. Short physical examinations will be done at the following time points:
    - on Day –1: at –24, –23, –22, –20 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 1, 2, 4, and 12 h after the morning dose
    - on Days 1 & 2: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.5, 1, 2, 4, 12, 24 h (Day 10), 48 h (Day 11), 72 h (Day 12) and 96 h (Day 13)
    - at outpatients visits on Days 17, 20, 23, 27, and at long-term follow-up visits (Days 60, 90 and 120) (± 2 days)
3. A full neurological examination will be done at screening Visit 1, before the morning dose on Day 0 and on Day 14 after the morning dose (120 h).
4. A short neurological examination will be given at the following time points:
    - on Day –1: at –24, -23, -22, -20, and -12 h before the morning dose on Day 0
    - on Day 0: at 1, 2, 4, and 12 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 1, 2, 4, 12, 24 (Day 10), 48 (Day 11), 72 (Day 12) and at 96 h (Day 13)
    - at outpatient visits on Days 17, 20, 23, 27 and at Follow-up (Day 30 ± 2 days), and long-term follow-up visits (Days 60, 90 and 120 ±2 days)

5. Ophthalmological examination will be performed at the second screening visit after all other eligibility criteria have been met, and on Day 10. If deemed necessary by the ophthalmologist, additional ophthalmology follow-up visit(s) may be scheduled for eye-related AEs. Subjects will be given the Ishihara test at screening visit 1.
6. Blood samples taken for glucose and insulin measurement will be used to complete an Oral Glucose Tolerance Test (OGTT). Samples taken will be:
    - on Day –2: at –48, –47, –46 and –44 h before the morning dose on Day 0
    - on Day 1: before and at 1, 2 and 4 h after the morning dose
    - on Day 8: before and at 1, 2 and 4 h after the morning dose
    - on Day 120 at 0, 1, 2 and 4 h timepoints relative to dosing

    Subjects will fast until completion of the OGTT test; lunch will be provided immediately afterwards
7. Blood samples for measurement of glucose, insulin, glucagon and cortisol will be taken:
    - on Day –1: at –24, –23, –22, –20 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 1, 2, 4 and 12 h after the morning dose
    - on Day 1: before the morning dose
    - on Day 9: before and at the following time points after the morning dose: 1, 2, 4, 12, 24 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14); and at follow up (Day 30 (± 2 days)). Subjects will fast for the Day 11, 12, 13,14 and 30 time points.

    Leptin and prolactin will also be measured at Screening Visit 1 and Day 9, as part of the insulin blood sample.
8. Administration of the study medicine will be done in fasting conditions on Days 0–9 at approximatively the same time each morning (±15 mins):
    - in Cohorts 1 & 2, emodepside will be giving in the morning only
    - in Cohort 3, emodepside will be given in the morning and evening (at 12 h intervals). On the last day (day 9), emodepside will be given only in the morning
9. 12-lead ECGs will be recorded in triplicate (with 1 minute between recordings) at –24 h (Day –1) before the morning dose on Days 0 and 9; single recordings will be made at all other time points. ECGs will be recorded:
    - at Screening Visit 1 and at Follow-up (Day 30 ± 2 days)
    - on Day –1: at –24, –23.5, –23, –22.5, –22, –21, –20, –16 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 0.5, 1, 1.5, 2, 3, 4, 8 and 12 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24 (Day 10), 72 (Day 12) and 120 h (Day 14) after the Day 9 dose

    Subjects should rest in the supine position for 10 minutes before ECG measurements.
10. Vital signs will comprise blood pressure (BP) and heart rate (HR) at all time points, with oral temperature included at screening and –24 h before the morning dose on Day 0 (Day –1). Subjects should rest in the supine position for 10 minutes before single BP and HR measurements are taken. Vital signs will be measured:
    - at the first screening visit and at Follow-up (Day 30 ± 2 days)
    - on Day –1: at –24, –23.5, –23, –22.5, –22, –21, –20, –16 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 0.5, 1, 1.5, 2, 3, 4, 8 and 12 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.5, 1, 1.5, 2, 3, 4, 8,12, 24, 36 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14)
    - at outpatients visits on Days 17, 20, 23 and 27 (± 2 days), and long-term follow-up visits (Days 60, 90 and 120 ±2 days)
11. Adverse event monitoring will be done throughout the study, but scheduled questioning will be done at the following time points:
    - at Screening Visit 1 and at Follow-up (Day 30 ± 2 days)
    - on Day –1, at -24, -23, -22, -21, -20, -18, -16, -12 h before the morning dose on Day 0

- on Day 0: before and at 1, 2, 3, 4, 6, 8 and 12 h after the morning dose
- on Days 1–8: before the morning dose
- on Day 9: before and at the following times after the morning dose: 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14)
- at outpatients visits on Days 17, 20, 23 and 27 (± 2 days), and long-term follow-up visits (Days 60, 90 and 120 ±2 days)

12. Blood samples for assay of emodepside in plasma will be taken:
    - on Day 0: before and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 15 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, 24, 36 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14)
    - at outpatients visits on Days 17, 20, 23 and 27 (± 2 days), and at Follow-up (Day 30 ± 2 days)

    Subjects should rest in the supine position for 10 minutes before blood is drawn (if possible).
13. Blood samples for assay of metabolites of emodepside in plasma will be taken:
    - on Day 0: before and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 15 h after the morning dose
    - on Day 9: before and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 15 h after the morning dose
14. Urine for assay of emodepside and its metabolites may be collected at the following time points:
    - On Day 0: from 0–4, 4–8, 8–12 and 12–24 h after the morning dose
    - On Day 9: from 0–4, 4–8, 8–12 and 12–24 h after the morning dose
15. Blood and urine samples for clinical laboratory safety tests (haematology, biochemistry, coagulation & urinalysis) will be taken: at Screening Visit 1; on Day –1 (–24 h before the morning dose on Day 0); before the morning dose on Day 0; before the morning dose on Days 1, 5 and 8; before, 24 h (Day 10) and 120 h after the morning dose on Day 9 (Day 14); at the Day 23 outpatient visit (± 2 days); at Follow-up (Day 30 ± 2 days); and at long-term follow-up (Days 60, 90 and 120 ± 2 days).

    Subjects should rest in the supine position for 10 minutes before blood is drawn (if possible).
16. Serology tests will comprise HIV 1 & 2, hepatitis B & C, and HbA1c
17. Blood samples for measurement of leptin and prolactin will be taken at Screening Visit 1 and before the morning dose on Day 9.
18. Subjects will be admitted to the ward on Day 119, before the Day 120 long-term follow-up visit.

5.2. Table 3: Schedule of events expanded view: pre-dosing period

	Pre-dosing period													
	Day –2				Day –1									
Procedure	**–48 h**	**–47 h**	**–46 h**	**–44 h**	**–24 h**	**–23.5 h**	**–23 h**	**–22.5 h**	**–22 h**	**–21 h**	**–20 h**	**–18 h**	**–16 h**	**–12 h**
Short physical examination[2]					X		X		X		X			X
Short neurological examination[4]					X		X		X		X			X
Oral Glucose Tolerance Test (OGTT)[6]	X	X	X	X										
Glucose, insulin, glucagon and cortisol[7]					X		X		X		X			X
12-lead safety ECGs[9]					X	X	X	X	X	X	X		X	X
Vital signs[10]					X	X	X	X	X	X	X		X	X
AE monitoring[11]					X		X		X	X	X	X	X	X
Laboratory safety tests[15]					X									

5.3. Table 4: Schedule of events expanded view: first dosing day

	First dosing day (Day 0)													
Procedure	**0 h**	**0.25 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**2.5 h**	**3 h**	**4 h**	**6 h**	**8 h**	**12 h**	**15 h**	**24 h**
Short physical examination[2]	X			X		X			X			X		
Full neurological examination[3]	X													
Short neurological examination[4]				X		X			X			X		
Glucose, insulin, glucagon and cortisol[7]	X			X		X			X			X		
Administration of emodepside[8]	X											X*		
12-lead safety ECGs[9]	X		X	X	X	X		X	X		X	X		
Vital signs[10]	X		X	X	X	X		X	X		X	X		
AE monitoring[11]	X			X		X		X	X	X	X	X		
PK of emodepside in plasma12[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	

	First dosing day (Day 0)													
Procedure	**0 h**	**0.25 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**2.5 h**	**3 h**	**4 h**	**6 h**	**8 h**	**12 h**	**15 h**	**24 h**
PK of metabolites of emodepside in plasma[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK of emodepside and metabolites in urine[1414]	←	———	———	———	———	———	———	———	———	———	———	———	———	→
Laboratory safety tests[15]	X													

* Group 3 only. Order of assessments at this time point is given in Section 8.2

5.4. Table 5: Schedule of events expanded view: last dosing day

	Last dosing day (Day 9)													
Procedure	**0 h**	**0.25 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**2.5 h**	**3 h**	**4 h**	**6 h**	**8 h**	**12 h**	**15 h**	**24 h**
Short physical examination[2]	X		X	X		X			X			X		
Short neurological examination[4]	X			X		X			X			X		
Glucose, insulin, glucagon and cortisol[7]	X			X		X			X			X		
Administration of emodepside[8]	X											X*		
12-lead safety ECGs[9]	X		X	X	X	X		X	X		X	X		
Vital signs[10]	X		X	X	X	X		X	X		X	X		
AE monitoring[11]	X		X	X		X		X	X	X	X	X		
PK of emodepside in plasma12[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK of metabolites of emodepside in plasma[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK of emodepside and metabolites in urine[1414]	←	———	———	———	———	———	———	———	———	———	———	———	———	→
Laboratory safety tests[15]	X													
Leptin and prolactin[7,17]	X													

* Group 3 only. Order of assessments at this time point is given in Section 8.2

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 randomised, whenever applicable.

Screening should occur between 3 and 28 days before the intended initiation of treatment: detailed procedures are described in Section 8: Study Assessments.

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 Generic Document Review Committee. The trial-specific information and consent form will be signed by the subject either before any screening evaluation or after the Investigator assesses the eligibility of the subject for the trial, and before the subject is randomised to receive the first dose of emodepside or placebo. 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 a 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 in the trial will be as shown in Table 6 . Subjects will be allocated to treatment (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 24 subjects are randomized.

7. Study treatments

Subjects in Cohorts 1–3 will be randomised to receive either emodepside LSF solution, or matching placebo solution. Subjects in Cohorts 1 and 2 will receive once-daily doses of LSF or placebo, and subjects in Cohort 3 will receive twice-daily doses of LSF or placebo, by mouth.

The planned treatments to be administered are described below in Table 6 .

7.1. Doses and treatment regimens

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

	Subject numbers[a]	Formulation and route of administration	Planned subjects	
			Emodepside	Matching placebo
Cohort 1	1001 – 1008	5 mg LSF solution OD, or placebo, by mouth	6	2
Cohort 2	2001 – 2008	10 mg LSF solution OD, or placebo, by mouth	6	2
Cohort 3	3001 – 3008	10 mg LSF solution BID, or placebo, by mouth	6	2

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

Subjects will receive the study medication according to fasting instructions given in Section 4.3: On dosing days, following an 9 h overnight fast (no food or drink, except water), Investigator site personnel will administer study medication (active or placebo) to subjects with 240 mL ambient temperature water.

Subjects in Cohort 3 will be given an evening dose approximately 12 h after their morning dose on Days 0–9: they'll fast for 2 h before and 1 h after that evening dose.

Study treatment will be administered under the supervision of Investigator site personnel, following site standard procedures to ensure treatment compliance.

7.2. Emodepside study treatment

Detailed information on the drug substance emodepside (BAY 44–4400) is given in the Investigator's Brochure.

The study treatment will be provided as 0.1% (w/v) emodepside oral (LSF) solution with 1 mg active pharmaceutical ingredient (emodepside, BAY 44-4400) per mL. It is available as bulk solution in a brown glass container with a dosing adapter and child-resistant screw cap closure.

Doses up to 20 mg, corresponding to 20 mL solution, can be dispensed from 1 bottle. The solution has to be withdrawn from the container using a syringe and is then administered directly from the syringe into the mouth of the subject. The solution should not be diluted before application. The solution may be used for application of doses up to a maximum of 20 mg per day corresponding to application of 20 mL of the solution per day, based on the results of the single-administration dose study (DNDI-EMO-001).

The solution is composed of the active substance emodepside and the following excipients:

- macrogol 400
- polysorbate 20
- levomenthol
- butylhydroxyanisole.

7.3. Placebo study treatment

A corresponding placebo solution is available with excipients matching the

emodepside treatment, but lacking the active pharmaceutical ingredient.

7.4. IMP supply and handling

Formulation and Supplier:

Emodepside will be supplied by the Sponsor, DNDi, as emodepside LSF solution and matching placebo solution.

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.

Preparation and Dispensing:

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

7.5. Dose escalation

During the study, the dose will be increased only if the safety, tolerability and PK of the previous dose are acceptable.

Dose escalation will be decided by the Safety Review Group (SRG) at the Safety Review Meeting (see Section 11). The dose will not be escalated until the SRG have reviewed the safety, tolerability and PK data until 48 h after the final dose of study medication in at least 4 subjects on active treatment (ie. at least 6 subjects overall) and agree that it is appropriate to give a higher dose; that decision will be taken in the Safety Review Meeting, before dosing of the subsequent cohort. The next planned dose level may be reduced, a dose level may be re-tested, or an intermediate dose level selected, based on the emerging data.

The dose level will not exceed 20 mg LSF oral solution (1 mg/mL) per day.

7.6. Study stopping criteria

7.6.1. Dose escalation stopping criteria

A dose level will not be repeated, or exceeded, if the results of safety tests give the Sponsor or Investigator cause for concern, or if one of the following dose escalation stopping criteria is met:

- any of the trial stopping criteria in Section 7.6.2 are met.
- the Investigator considers the dose level to be not well tolerated.
- predicted mean plasma concentrations in the subjects at the next scheduled dose level exceed or equal:
    - C_{max}: 612 µg/L

  (based on the highest dose in the Single-Ascending Dose (SAD) study: DNDI-EMO-001)

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

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 AEs 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 further exploring the relationship between dose and AE. If, in the judgement of the SRG, it would not be reasonable to expose more subjects to the level of discomfort experienced by those 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 AE and dose (or plasma concentration) of drug.

7.6.2. Trial stopping criteria

The trial will be stopped if either of the following occurs:

- one or more serious AE that is considered to be related to emodepside; or
- 2 or more subjects with a severe or clinically significant AE, considered to be related to emodepside, that occurs in the same treatment group

If, after an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the MHRA and REC. The trial will not restart until the amendment has been approved by the MHRA and REC.

7.7. Study treatment labelling, packaging

Emodepside supplied by the Sponsor will be manufactured, packed, labelled 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.

7.8. Accountability

All study treatments must be kept in a locked room that can be accessed only by the pharmacist or the Investigator. The study treatments must not be used for other purposes other than this protocol. Under no circumstances the Investigator or site staff may supply study treatments to other Investigators or sites, or allow the medications to be used other than as directed by this protocol without prior written authorization from DNDi. Adequate records on receipt, use, return, loss, or other disposition of treatments must be maintained.

Upon receipt of the study drugs, the Investigator or a relevant member of the pharmacy/pharmacy delegate, will send the Sponsor the corresponding acknowledgement of receipt form. This form must be filled (including the date of receipt) and signed by a relevant member of the pharmacy/pharmacy delegate, or the Investigator. An audit trail of all medication transported and dispensed during the study will be maintained.

All investigational materials (medication and packaging) unused in the study will be destroyed by HMR (with the Sponsor's approval), or 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.

The study drug will be dispensed only under the restricted conditions defined in the present protocol and the Pharmacy Manual/Study Procedures Manual. Drug will be administered by the Investigator only or his/her delegate.

Time of administration and initials of the person administering the study medication will be documented in the Case Report Form (CRF).

7.9. Storage

Emodepside oral solutions (active and placebo) should be stored at 2–8°C in the original container (upright storage).

7.10. Blinding and procedures for unblinding

The study drug and matching placebo will be identical in appearance in order to preserve the single blind with respect to the subject; the subjects are blinded and will not know which treatment (active or placebo) they are given. The Investigator (including clinical, statistics and data management personnel) and the Sponsor (including the study monitor) will remain blinded during each cohort, so as not to potentially introduce bias, unless safety concerns necessitate unblinding (if the knowledge of the treatment administered is useful for the best medical care of an AE). Investigator pharmacy staff, who'll dispense the IMP, will not be blinded at any time.

For safety and dose escalation purposes, the data may be unblinded at the end of each cohort for review by the SRG. 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.

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.

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 the database is locked at the end of cohorts 1 and 2 and again at the end of cohort 3, 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 randomisation code is broken, the reason will be fully documented and entered in source documents and the CRF.

7.11. Concomitant treatments

Prior therapy as indicated in the exclusion criteria (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 2000 mg 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 drug at the discretion of the Investigator and the Sponsor, if use of that medication could compromise the safety of the subject or the scientific value of the trial, and will be followed up until the end of the study. No dietary supplements or herbal remedies that 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. Further questions about concomitant medication can be directed to the Sponsor's Medical Expert.

Use of any concomitant medication will be recorded until the last long-term follow-up visit 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 Assessments

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 the Subject Information and Consent Form (ICF).

8.2. Timing of Assessments

All procedures will be conducted according the Schedule of events, in Section 5.

General order of assessments

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:

- Neurological examination and physical examination
- 12-lead ECGs: after 10 minutes rest in the supine position single readings, with the exception of one triplicate reading
- Blood pressure/heart rate: after 10 minutes rest in the supine position
- AE monitoring (spontaneous and solicited AE monitoring will include specific questioning for tolerability and safety)
- PK blood sampling (taken at, or closest to, the nominal time point)
- PK blood sampling for metabolites
- Blood sampling for profiles of glucose, insulin, glucagon, and cortisol; single samples for prolactin and leptin; Laboratory safety blood samples. Urine samples will be collected when possible (dependent on the subject) but within the allowed deviation times.

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 those 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 8.4 of this protocol.

To minimise variability, throughout the study, study staff should also ensure a minimum 10-minute supine period, where possible, before drawing any blood samples (including lab safety assessments).

Throughout the study (from subject signature of the ICF) 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, at long-term follow-up, and at the specific time points detailed in the Schedule of events (Section 5).

8.3. Study visits

Baseline will be considered as the last assessment performed prior to randomisation.

8.3.1. Screening Visit 1

All subjects will be screened within the 28 days before administration of the study medication to confirm that they meet the subject selection criteria for the study. Subjects who fail screening by not meeting the inclusion and/or exclusion criteria may be rescreened at the Investigator's discretion.

Subjects will attend the ward, having fasted overnight for at least 10 h.

The following assessments will be done in order to collect historical safety data, and to assess eligibility for the study:

- Review of inclusion and exclusion criteria
- Complete medical history: including demographic data, previous and concomitant medications (ie, prescription medicine taken within 28 days, or non-prescription drugs and dietary supplements taken within 7 days, before the planned first dose, and/or plan to continue taking throughout the study)
- Full physical examination: see Section 8.5.3. A detailed description of the physical examination will be included in the Study Procedures Manual
- Full neurological examination: see Section 8.5.3. Also a detailed description of the neurological examination will be included in the Study Procedures Manual. Subjects will be given the Ishihara colour perception eye test.
- Body weight and height, vital signs (oral temperature, blood pressure and heart rate will be determined; see Section 8.5.2)
- 12-lead ECGs
- AE monitoring (spontaneous and solicited AE monitoring will include specific questioning for tolerability and safety)
- Urinary drugs of abuse screen (opiates, amphetamines, barbiturates, cannabis, benzodiazepines and cocaine-metabolites) and breath test for alcohol
- Blood sampling for serology (HIV and hepatitis) and for Hb1Ac
- Blood sampling for clinical safety laboratory evaluations:
    - Haematology and coagulation: haemoglobin, haematocrit, 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
    - Leptin and prolactin
- Urinalysis for clinical laboratory safety evaluations, via dipstick test: glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites

All biological assessments will be performed in fasting state (at least 9 h), and with a 10 minute supine rest before sampling.

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 ophthalmology clinic for Screening Visit 2.

8.3.2. Screening visit 2: Ophthalmological assessment

Details of the ophthalmological assessment are given in Section 8.5.4. Screening

Visit 2 will take place after confirmation that all other eligibility criteria have been met and may take place up to and including Day –3.

Subjects will be scheduled to report to the Investigator site for admission to the ward on Day –3.

8.3.3. Admission to Ward (Day –3)

Subjects will be admitted to the ward at the Phase 1 Unit, on Day –3 at approximately 1600 h, and will have a urinary drug screen and alcohol breath test, and be monitored for AEs.

Subjects will fast overnight from 2300 h until after their assessments are complete on the morning of Day –2 (about 13 h in total).

8.3.4. Day –2

Blood samples will be taken for measurement of glucose and insulin for the OGTT at times as per the Schedule of events in Section 5.

Subjects will be given a high glucose liquid to drink after their first sample (–48 h) is taken. The glucose and insulin measurements taken at 1, 2 and 4 h after the –48 h sample (–47, –46 and –44 h) will be used to complete the OGTT. After those samples are taken, subjects will have their first meal of the day. Subjects will be monitored for AEs.

Subjects will fast overnight for at least 9 h before the –24 h time point on Day –1, until at least the –20 h timepoint on Day –1.

8.3.5. Pre-day (Day –1)

On the morning of Day –1, a cannula will be inserted into a forearm vein, under local anaesthesia with lidocaine 0.5%, for withdrawal of venous blood (for glucose, insulin, glucagon and cortisol measurements).

Subjects will have the following procedures completed as scheduled in Section 5, time-matched to Day 0:

- Scheduled AE monitoring
- Short physical examination and neurological assessments (including body weight, once in the morning)
- 12-lead ECGs (in triplicate only at –24 h)
- Vital signs (including oral temperature)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis)
- Blood samples will be taken for measurement of glucose, insulin, glucagon and cortisol

Subjects will fast overnight as described in Section 4.3.

8.3.6. Profile day (Day 0)

Eligibility (based on inclusion and exclusion criteria) must be determined before

subject randomisation.

On the morning of Day 0, a cannula will be inserted into a forearm vein, under local anaesthesia with lidocaine 0.5%, for withdrawal of venous blood. The following will be done within 0.75 h before the morning dose of study medication and at the time points after administration outlined in the Schedule of Events (Section 5):

- Scheduled AE monitoring (particularly any event related to the CNS)
- Neurological examinations – full before the morning dose, and short at all other time points
- Short physical examinations
- 12-lead ECGs (in triplicate only at the pre-dose measurement)
- Vital signs (BP and HR)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis)
- Blood sampling to assay glucose, insulin, glucagon and cortisol
- Blood sampling to assay pre-dose emodepside and its metabolites in plasma (with frequent sampling after dosing)

Subjects in Cohort 3 will have an additional evening dose of the study medication, approximately 12 h after their morning dose.

Subjects will fast overnight, each night, as described in Section 4.3.

8.3.7. Repeat dosing period (Days 1–8)

Subjects will have the following assessments at the time points specified in the Schedule of Events (Section 5):

- Scheduled AE monitoring (particularly any event related to the CNS)
- Short neurological examination
- Physical examination – full on Days 3–8 and short on Days 1 and 2
- 12-lead ECGs (single measurements)
- Vital signs (BP and HR)
- Blood sampling for the OGTT (Days 1 and 8 only). Subjects will be given a high glucose liquid to drink after their first sample is taken, as done on Day –2.
- Blood sampling to assay glucose, insulin, glucagon and cortisol (Day 1 only)
- Blood sampling to assay pre-dose emodepside in plasma
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis), on Days 1, 5, and 8 only

Subjects will fast overnight, as described in Section 4.3.

8.3.8. Profile day (Day 9)

On the morning of Day 9, a cannula will be inserted into a forearm vein, under local anaesthesia with lidocaine 0.5%, for withdrawal of venous blood. The following will be done within 0.5 h before the morning dose of study medication and at the time points after administration outlined in the Schedule of Events (Section 5):

- Scheduled AE monitoring (particularly any event related to the CNS)
- Short neurological and physical examinations
- 12-lead ECGs (in triplicate only at the pre-dose measurement)
- Vital signs (BP and HR)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis)
- Blood sampling to assay glucose, insulin, glucagon, cortisol
- Blood sampling to assay leptin and prolactin
- Blood sampling to assay pre-dose emodepside and its metabolites in plasma

Subjects in Cohort 3 will have a final morning dose of the study medication only on Day 9.

Subjects will fast overnight, as described in Section 4.3.

8.3.9. Days 10–14

Subjects will remain on the ward for another 5 days, and have the following assessments at the time points outlined in the Schedule of Events (Section 5):

- Scheduled AE monitoring (particularly any event related to the CNS)
- Physical examination and neurological assessments – short on Days 10-13 and full on Day 14
- Ophthalmological assessments (Day 10 only)
- 12-lead ECGs (single measurements; on Days 10, 12 and 14 only)
- Vital signs (BP and HR)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis) (on Days 10 and 14 only)
- Blood sampling to assay glucose, insulin, glucagon and cortisol
- Blood sampling to assay post-dose emodepside in plasma

Subjects will fast during this period as described in Section 4.3.

Subjects may be discharged from the ward following completion of their Day 14 assessments.

8.3.10. Outpatient Visits (Days 17, 20, 23 and 27), Follow-up Visit (Day 30), and long-term follow-up Visits (Days 60, 90 and 120) ± 2 days

Subjects will return to the clinic for each ambulatory visit, and the Follow-up visit, as scheduled in the Schedule of events (Section 5), to have some or all of the following procedures:

- Scheduled AE monitoring (particularly any event related to the CNS)
- Physical examination – short on Days 17, 20, 23, 27, 60, 90 and 120, and full at Day 30
- Short neurological assessments
- Vital signs (BP and HR)
- 12-lead ECGs (single measurements)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis) on Days 23, 30, 60, 90 and 120 only (haematology will include HbA1C on Day 120 only)
- Blood sampling to assay post-dose emodepside in plasma
- Alcohol breath tests on Days 60, 90 and 120 only
- Blood sampling for the OGTT (Day 120 only). Subjects will be given a high glucose liquid to drink after their first sample is taken, as done on Days –2, 1 and 8.

Subjects will fast overnight before their Day 23 and Day 30 visit, and all long-term follow-up visits, as described in Section 4.3.

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

Subjects who terminate the study early will have the same assessments as at follow-up (Day 30).

Subjects will be admitted on Day 119, before their Day 120 long-term follow-up visit.

8.4. Assessments

8.4.1. 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 emodepside 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 8.4.4, unless in the opinion of the Investigator, it's in the subject's best interest that extra blood is taken for additional safety tests.

An additional 48 h' residence on 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 are needed.

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

- Deviations of not more than 5 min on measurements scheduled up to and including 4 h after a morning dose;
- Deviations of not more than 15 min on measurements scheduled from after 4 h to 24 h after a morning dose;
- Deviations of not more than 1 h on measurements scheduled more than 24 h after a morning dose; and
- Deviations of not more than 2 days on measurements scheduled for outpatient visits, the Follow-up visit, and long-term follow-up visits.

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	Days 0–9	
Pre –24 h	Pre-dose (0 h)	Within 75 min before
–24 h to –23.5 h	Up to and including 30 min after the morning dose	± 5 min
After –23.5 h to –20 h	After 30 min to 4 h after the morning dose	± 10 min
After –20 to –12 h	After 4 h to 24 h after the morning dose	± 15 min
NA	more than 24 h after the morning dose	± 1 hour[2]

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. Deviations at outpatients visits (during Days 15 to 30) are ± 2 days, as shown in the in Schedule of events (Section 5)

8.4.2. PK assessments

Blood samples assaying the concentration of emodepside and its metabolites in plasma will be collected at the time points indicated in the Schedule of events (Section 5). 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 will be collected either by cannulation or by venepuncture. 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. Blood volumes for PK samples are shown in Section 8.4.4.

Plasma will be analysed 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 Days (Day 0 and Day 9), frequent blood samples will be collected for PK estimation and emodepside plasma concentrations. On each treatment period, the following PK parameters of emodepside will be derived for each subject:

Single Dose Day 0 parameters

AUC_{12}	The area under the concentration-time curve from time zero (pre-dose) to 12 h will be calculated using a trapezoidal method.
AUC_{24}	The area under the concentration-time curve from time zero (pre-dose) to 24h will be calculated using a trapezoidal method.
AUC_{12}/D	The area under the concentration-time curve from time zero (pre-dose) to 12 h, corrected for dose
AUC_{24}/D	The area under the concentration-time curve from time zero (pre-dose) to 24h, corrected for dose
$AUC_{12,norm}$	The area under the concentration-time curve from time zero (pre-dose) to 12 h corrected by dose and body weight
$AUC_{24,norm}$	The area under the concentration-time curve from time zero (pre-dose) to 24h 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_{last}	Mean Residence Time from time zero (pre-dose) to the time of last quantifiable concentration will be calculated using $$MRT_t = \frac{AUMC_t}{AUC_t}$$ Where $AUMC_t$ is the area under the first moment of the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration
V_z/F	Apparent volume of distribution will be calculated using the following formula: $$V_z / F = \frac{Dose}{\lambda_z \bullet AUC_\infty}$$

Multiple Dose Day 9 parameters

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: $t_{1/2} = \ln 2 / \lambda_z$.
$t_{1/2,dom}$	The dominant half-life will be calculated from the terminal slope of the log concentration-time (0-24h) curve according to the following equation: $t_{1/2,dom} = \log_e 2 / \lambda_z$
AUC_{last}	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_{last}/D	The area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration, corrected for dose.
$AUC_{last,norm}$	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_{12}	Area under the plasma concentration-time curve during a 12 h dosing interval
AUC_{12}/D	Area under the plasma concentration-time curve during a 12 h dosing interval corrected for dose
$AUC_{12,norm}$	Area under the plasma concentration-time curve during a 12 h dosing interval corrected by dose and body weight
AUC_{24}	Area under the plasma concentration-time curve during a 24 h dosing interval
AUC_{24}/D	Area under the plasma concentration-time curve during a 24 h dosing interval corrected for dose
$AUC_{24,norm}$	Area under the plasma concentration-time curve during a 24 h dosing interval corrected by dose and body weight
AUC_{∞}	The area under the plasma drug concentration vs. time curve from time zero to infinity.
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
$\%AUC_{extrap}$	Percentage of AUC_{∞} extrapolated from from t_{last} to infinity, using the following formula $$\%AUC_{extrap} = \frac{100 \times AUC_{t-\infty}}{AUC_{\infty}}$$
$C_{max,ss}$	The observed maximum plasma concentration measured in a subject at steady state, identified by inspection of the drug concentration vs. time data.
$C_{max,ss}/D$	The observed maximum plasma concentration measured in a

subject at steady state, identified by inspection of the drug concentration vs. time data, corrected for dose.

$C_{max,ss,norm}$ The observed maximum plasma concentration at steady state, 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 extrapolated to infinity

CL_{ss}/F Apparent total clearance from plasma at steady state will be calculated using the following formula:

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

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

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

$RA(C_{max})$ Accumulation ratio for $C_{max,}$ calculated from C_{max} at steady state and C_{max} after single dose

$RA(AUC_{tau})$ Accumulation ratio for AUC_{tau}, calculated from AUC_{tau} at steady state and AUC_t after single dose, where t = tau.

Steady state (days 1 – 9)

C_{trough} Trough plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration]) obtained directly from the concentration-time data.

8.4.3. PD assessments

Blood samples for the determination of levels of glucose, insulin, glucagon and cortisol, and prolactin and leptin (Days −1 and 9 only) will be collected from each subject during the study, at the time points indicated in the Schedule of events (Section 5). In addition, glucose and insulin measurements will be used in the OGTT on Days –2, 1, 8 and 120.

The exact date and time of sampling will be recorded in the CRF. Blood volumes for those samples are shown in Section 8.4.4.

Collection of samples for pharmacodynamic assessments: Blood for glucose, insulin, cortisol, prolactin and leptin will be collected in serum-separating tubes (SST) with a gelatin plug. Samples will then be transferred to the laboratory.

8.4.4. Total blood volume

The blood volume planned to be collected from each subject during the course of this study is detailed in Table 4 . Additional samples may be required in the event of AEs. The total blood volume to be taken during the study will be 538.5 mL.

Additional blood may need to be collected for assay of emodepside, its metabolites, or for laboratory safety tests. No more than an extra 50 mL blood will be taken.

After collection, samples (blood and urine) may be stored for up to approximately 12 months after end of study before being destroyed.

Table 4 . Blood volumes for Cohorts 1–3

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Haematology	14	2	28
Hb1Ac	2	2	4
Biochemistry including free T3 and T4, and glucose	40	2.5	100
Coagulation	14	3	42
Serology	1	2.5	2.5
Insulin, cortisol and prolactin	23	2.5	57.5
Glucagon	22	2	44
Leptin	2	2.5	5
Emodepside PK[a]	45	3	135
Metabolites of emodepside	26	5	130
		Total	**548 mL**

[a] optional samples can be taken from PK blood collections in up to 3 cohorts, to cover a whole PK profile. Those samples may be retained for possible future bioanalytical method development. No additional blood will be collected for those optional samples.

After each blood sample, the cannula will be flushed with 3–5 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 2 mL will be drawn via the cannula into the sampling syringe, and immediately re-injected gently via the cannula. The definitive blood sample will be taken after a 10-second delay.

8.5. Assessment of Safety

Safety of the treatments will be assessed through routine monitoring of AEs.

From screening (for AE onset after the subject signs the ICF), daily during the in-patient phase, then at each visit, and at the Follow-Up and long-term follow-up Visits, the patients will be asked about current AEs or any events observed during the period previous to the visit.

In addition, 12-lead ECG recording, regular measurement of vital signs and

neurological and physical examinations, ophthalmological evaluation, clinical laboratory parameters monitoring, will be made at scheduled follow-up visit. (see Section 8.6.1 for AE recording and reporting) and as described below. At long-term follow-up visits, there will be a short physical examination and clinical laboratory parameters will be monitored.

8.5.1. 12-lead ECG Safety recording

Standard 12-lead ECGs will be recorded as per the Schedule of events in Section 5. 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. Any ECG abnormality confirmed by repeat will be assessed for clinical significance and if so reported as an AE (see AE definition in Section 8.6.1). If out of range at screening, the ECG may be repeated once.

8.5.2. Vital signs

Blood pressure and heart rate will be measured, in the supine position after 10 minutes rest, at times detailed in the Schedule of events (Section 5).

Oral temperature will be measured at screening and on Day −1 (24 h before the morning dose on Day 0).

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

Oral temperature will be measured using oral thermometers

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

- Supine systolic BP: 90–140 mm Hg
- Supine diastolic BP: 40–90 mm Hg
- Supine heart rate: 40–100 beats/min
- Oral temperature: 35.5–37.8°C

If the result of the repeat measurement is still out of range, the Investigator will make an assessment of clinical significance (if the abnormality is assessed as clinically significant, it will be reported as an AE) and decide on an appropriate course of action. If out of range at screening, vital signs may be repeated once.

8.5.3. 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 (see below).

Height and body weight will also be measured (at screening) and body weight only on the morning of Day −1. At certain time points, as detailed in the Schedule of events (Section 5), a short physical examination will be performed (to be detailed in the Study Procedures Manual).

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 full and short neurological exams will be in the Study Procedures Manual. Abnormalities assessed as clinically significant will be reported as AE (see AE definitions in Section 8.6.1).

8.5.4. Ophthalmological examination (Screening Visit 2 and Day 10)

For Screening Visit 2, subjects will attend a specialist eye hospital for ophthalmology assessments (see Section 8.3.2) to be performed by a Consultant Ophthalmologist (and described in the Study Procedures Manual).

Subjects will be informed that they will need to bring their distance glasses (if applicable) and that, at Screening Visit 2, their near vision will be blurred for approximately 2 h (due to the use of mydriatic eye drops) following the eye-testing procedures. Abnormalities assessed as clinically significant will be reported as AE (see AE definitions in Section 8.6.1).

Subjects will also have an ophthalmological assessment on Day 10.

8.5.5. Clinical Laboratory Safety Assessments

Processing of samples will be done by the HMR Analytical Laboratory in accordance with the laboratory's standard operating procedures, and additional information may be found in the Study Procedures Manual.

The HMR Analytical Laboratory will do safety tests on blood and urine samples using instruments interfaced to a validated laboratory information management system (LIMS). Confirmed abnormal laboratory results (after repeat) will be assessed for clinical significance (CS; see CS assessment below) and reported as AEs if necessary (see AE definition in Section 8.6.1). Data from analysers that are not interfaced will be entered manually into the LIMS.

Collection of samples for laboratory safety tests: Blood will be taken for haematology (2 mL in EDTA), and biochemistry and serology (2 × 2.5 mL in tubes with a gelatin plug). Blood will be taken to measure Hb1Ac (2 mL in EDTA), and for coagulation (3 mL in sodium citrate). Blood samples will be collected into 13 × 75 mm tubes. Urine will be collected in Universal containers. Samples will then be transferred to the laboratory.

Laboratory abnormalities considered AEs:

Laboratory abnormalities assessed as "clinically significant" have to be reported as an AE (refer to AE definition in section 8.6.1) only if they meet at least one of the following conditions:

- The abnormality suggests a disease and/or organ toxicity AND this abnormality was not present at the screening visit, or is assessed as having evolved since the screening visit
- The abnormality results in discontinuation of the study drug
- The abnormality requires medical intervention or concomitant therapy

When reporting an abnormal laboratory result, a clinical diagnosis should be recorded rather than the abnormal value itself, if available (for example, "anaemia" rather than "decreased red blood cell count")

8.6. Adverse Event definitions and reporting

8.6.1. Adverse Event definitions

An *adverse event* will be defined as:

Any untoward medical occurrence in a clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with that treatment. An AE 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, ophthalmologic or neurological examination etc.) or laboratory results which are assessed as "clinically significant". Information on AEs must be evaluated by a physician.

What is not an AE?

- Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are NOT considered as AEs.

8.6.2. Serious Adverse Event (SAE)

An AE will be defined as serious if it is

- **results in death**

  ie Causes or contributes to the death.

- **is life-threatening**

  Refers to an AE in which the subject was at risk of death at the time of the AE; it does not refer to an AE that hypothetically might have caused death if more severe.

- **requires in-patient hospitalisation or prolongation of existing hospitalisation**

  ie The AE requires at least an overnight admission or prolongs a hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (ie. plastic surgery) or per protocol or for normal disease management ((including treatment adjustment) are NOT to be considered as SAE according to this criterion (ie. if the protocol requires planned hospitalisation).

- **results in persistent or significant disability or incapacity**

  ie The AE resulted in a substantial disruption of the subject’s ability to conduct normal activities.

- **is an important medical event, i.e. is medically significant.**

  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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious AE/reaction.

8.6.3. Eliciting Adverse Event information

The Investigator is required to report all directly observed AEs and all AEs spontaneously reported by the trial subject using concise medical terminology.

In addition, each trial subject will be questioned about the occurrence of AEs using non-leading questions (eg. "How are you feeling?"), at times specified in the Schedule of events (Section 5).

Each AE will be assessed for severity, and causality (see definitions in Section 8.6.6 and 8.6.7). In addition, each AE is to be classified by the Investigator as serious or non-serious (see definition in Section 8.6.2). This classification will determine the reporting procedure for the event (see Section 8.6.5).

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.

Non-serious AEs are to be reported on the CRF, which is to be submitted to DNDi as specified in Section 12.2. In the CRF, a given AE will be recorded only one time per subject, and the severity recorded will be the maximum level reached. If several distinct episodes of the same condition occur, their number will be recorded in the CRF.

SAEs will be reported both on the AE CRF and the SAE forms.

8.6.4. Adverse Event reporting period

The AE reporting period begins upon subject enrolment in the trial (after signature of the ICF) and ends at the last Long-term Follow-up Visit (Day 120 ±2 days).

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 possibly related to the investigational medicinal product should also be reported as an AE.

8.6.5. Serious Adverse Event reporting requirements

All serious adverse events (SAE) are to be reported immediately (within 24 hours of awareness of SAE by the Investigator) to the Sponsor Clinical Team (via SAEEMOHVstudies@dndi.org), and to DNDi Pharmacovigilance (via pharmacovigilance@dndi.org), using the SAE report form. This includes a

description of the event, onset date and type, duration, severity, 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.

SAEs should also be reported on the clinical trial AE case report form (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 addition to immediately reporting SAEs to DNDi, **the Investigator will immediately notify the 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 Research Ethics Service (RES).

A **suspected unexpected serious adverse reaction (SUSAR)** is a suspected adverse reaction related to an investigational medicinal product (as defined in Section 8.6.7) that is both unexpected and serious.

DNDi is responsible for determining the expectedness of the 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 SUSARs, and will be responsible for ensuring that the 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 calendar days after DNDi becomes aware of the event. Follow-up reports should be provided within another 8 calendar days.
- Other SUSARs must be reported to the REC and MHRA/EMA within 15 days after DNDi becomes aware of the event.

8.6.6. Grading of Adverse Event severity

The Investigator will use the terminology MILD, MODERATE, or SEVERE to describe the maximum severity of the AE. This information will be entered in the AE case report forms. For purposes of consistency, these severity grades are defined as follows: Severity is a clinical determination of the intensity of an AE to describe its maximum severity. Please note the distinction between severity and seriousness of AEs. A severe AE is not necessarily a serious AE.

MILD	Does not interfere with subject's usual functions. 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	Interferes to some extent with subject's usual functions. The subject experiences sufficient discomfort to interfere with or reduces his or her usual level of activity.
SEVERE	Interferes significantly with subject's usual functions. The subject is unable to carry out usual activities and/or the subject's life is at risk from the event.

8.6.7. Adverse Event causality assessment

For both serious and non-serious AEs, the Investigator is required to assess if there is a causal relationship between the AE and the study drug, ie. to determine whether there exists a **reasonable possibility** that the study drug caused or contributed to the AE.

To help Investigators with the decision binary tree in the evaluation of causality, the CIOMS VI group recommends that Investigators be asked to consider the following before reaching a decision:

- Medical history (including presence of risk factors)
- Lack of efficacy/worsening of existing condition
- Study medications
- Other medications (concomitant or previous)
- Withdrawal of study medication, especially following trial discontinuation / end of study medication
- Erroneous treatment with study medication (or concomitant)
- Protocol related procedure

The decision to suspend, resume, or permanently interrupt treatment due to an AE will be left to the clinician in charge.

The following categories for relationship to treatment will be used during AE reporting:

Related	There is at least a reasonable possibility of a causal relationship between an AE 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.

The following categories will be used to document outcome of each AE:

Action taken:	None, drug treatment, subject withdrawn, other (specified).
Outcome:	Completely recovered; recovered with sequelae; ongoing; death; unknown

8.6.8. Exposure in utero

Not applicable for this trial (subjects are all male). Study subjects must use contraceptive method (condoms) from first dose of study drug to 120 days after the last dose of study drug.

Should their female partner become pregnant despite this preventive measure, the following instructions must be followed:

All pregnancies started in partners of trial subjects within 120 days after administration of the last dose of IMP to the study male healthy subject, should be reported using the Pregnancy form (as per the same process and timelines for SAEs) and consent from the subject's partner sought to follow-up the outcome for the new

born (up to the age of 2 years).

This must be done irrespective of whether an AE has occurred. The information submitted should include the anticipated date of delivery.

The investigator will follow the subject's partner until completion of the pregnancy or until pregnancy termination (ie. induced / spontaneous abortion). The investigator will provide pregnancy outcome information in the Child report form. In the case of a live birth, a paediatrician should assess the infant at the time of birth and submit a Child report, and the new born will be followed up to the age of 2 years.

Pregnancies are not considered to be a SAE.

An SAE should be declared in the case of unfavourable pregnancy outcome (abortion, still birth) or congenital abnormality.

In addition, pregnancies considered related to study treatment by the Investigator (ie. resulting from a drug interaction with a contraceptive medication) are considered as AEs and should be recorded on the AE pages of the CRF.

If this might be considered as an AE and assessed as a serious one, an SAE form is to be completed in addition to these two forms.

8.6.9. 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 their follow-up visit is complete, or otherwise the last contact with the subject).

In addition, all SAEs (related or not), and those non-serious events assessed by the Investigator as having a reasonable possibility of 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." The outcome of these events is to be documented on the CRF and SAE form (if required).

9. Withdrawal criteria

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, behavioural, 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 subject consent. The Sponsor may retain and continue to use any data collected before any 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 AE, thorough efforts should be made to clearly document the outcome of that AE.

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

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 (Day 30 ±2 days) (See the Schedule of events (Section 5)).

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 will be withdrawn from the study drug and followed up until resolution of the adverse event.

- ALT ≥ 5 x Upper Limit of Normal (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).

Note that all AEs must nevertheless be reported and followed-up as per Section 8.6(unless the subject withdraws consent for further assessments).

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, must not receive another dose of IMP, but can continue in the study and be monitored until the last long-term Follow-Up visit, or followed up until resolution of the adverse event, as specified in Section 8.6.9, whichever applies.

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

- AEs 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.

A subject should be withdrawn from the study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the subject.

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.

10.1. Sample size determination

No formal statistical sample size estimation has been performed, due to the exploratory nature of this study.

Missing data will be described in the Statistical Analysis Plan (SAP).

6 subjects per dose level (cohort) is considered sufficient to examine the safety and tolerability of emodepside, as well as the pharmacokinetics after single and multiple doses. Subjects who withdraw, or are withdrawn from the study, may be replaced at the discretion of the investigator upon consultation with the sponsor.

Interim analyses will be performed: after each dose, a safety assessment will be made using the primary PK parameters, AEs, vitals, ECGs, safety lab measurements, glucose and insulin measurements, and any abnormal findings. An additional interim analysis (including interim database lock) will be performed after Cohorts 1 and 2 have completed, to evaluate the progression into later phase studies.

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 analysed.
- 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.

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.

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. Demographics and Other Baseline Characteristics

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

Subjects who take concomitant medication will be listed. All non-trial medication will be coded using the World Health Organisation Drug Dictionary (WHO DD).

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

10.6. Safety Analysis

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

- Vital signs;
- 12-lead ECG;
- Haematology;
- Clinical chemistry;
- Coagulation;

- Urinalysis;
- Physical examination;
- Neurological examination;
- Ophthalmology assessments;
- AEs.

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

10.6.1. Vital signs, 12-lead ECG safety parameters

Vital signs at each planned assessment, and change in vital signs from baseline at each planned post baseline assessment (with or without potential clinical significance), 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.

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

QT, QTcB or QTcF > 450 msec and increases in QT, QTcB or QTcF from baseline (Day 0 pre-dose) of > 30 msec will be considered to be potentially clinically important. The number of subjects with a potentially clinically important QT, QTcB or QTcF will be summarised by actual treatment and time point, giving the numbers of subjects with QT, QTcB or QTcF > 450 msec, > 480 msec and > 500 msec, and the numbers of subjects with increases in QT, QTcB or QTcF from baseline of > 30 msec and > 60 msec (ICH Tripartite Guideline, 1998). 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.

10.6.2. Haematology and Clinical Chemistry Parameters

Data from haematology, coagulation 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.

10.6.3. Urinalysis parameters

These parameters will be individually listed and summarized.

10.6.4. Physical and neurological examination

An individual data listing of abnormal physical and neurological examination findings (with or without clinical significance) will be provided.

10.6.5. 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 12.2.

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

All AEs 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 AEs and the number of subjects with AEs will be summarised 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 maximum causality, for each system organ class and preferred term. AEs with missing severity and/or causality will be treated as severe and possibly related, respectively.

AEs leading to withdrawal, deaths and SAEs will be listed separately (fatal events will be listed separately from non-fatal events).

10.7. 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 (ICH Guidance For Industry E14, 2005); 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.

Plasma concentrations and PK parameters of emodepside and metabolite (if available) will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented

graphically.

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

10.8. 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.

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 medically-qualified Sponsor representative. Optionally, independent advisor(s) may be appointed to advise on dose escalation decisions, if required. Those meetings will follow DNDi SOP CL 26 (Safety Data Review during Phase I clinical trial) and will be described in the Safety Review Group charter.

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 SAE/query forms, REC 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 defined 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 into the Database.

12.3. Source documents

The verification of the CRF/SAE/pregnancy/child and query data must be by direct inspection of source documents. Source documents include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrolment logs.

The Investigator must maintain source documents such as laboratory and consultation reports, history and physical examination reports, etc., 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 25 years 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.

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, audits and inspections

Monitoring visits to the trial site will be made periodically by DNDi representatives or designated clinical monitors to ensure that GCP and all aspects of the protocol are followed. Source documents will be reviewed for verification of consistency with data on CRFs, and SAE/pregnancy/child and query forms. The Investigator will ensure direct access to source documents by 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 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. The inspections 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 and SAE/pregnancy/child/query forms, 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. Four visit types are planned: pre-study, study start, during the study, and study end. Visits may also be performed by regulatory authorities.

It will be the clinical monitor's responsibility to inspect the CRF and SAE/pregnancy/child/query forms 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 Research Ethics Committees (REC).

The Investigators will permit representatives of DNDi and/or designated clinical monitors to inspect all CRFs/SAE/pregnancy/child/query forms, 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

The data will be securely stored within HMR.

After the CRF has been completed and monitored by the clinical monitor, CRFs will be collected and data will be entered onto a database using double independent data entry. The trial data will be stored in a computer database maintaining confidentiality in accordance with national data legislation.

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

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.

The database will be locked after all the following have been completed: all expected CRF data have been entered and accounted for; all discrepancies have been resolved; data have been coded as appropriate; SAEs have been reconciled between the clinical database and DNDi safety database; all site audit findings impacting the database have been closed; and QC inspection has been completed.

Data in source documents 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. If requested, the investigator will provide the sponsor, MHRA, and REC with direct access to the original source documents.

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 Sponsor 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. All protocol modifications must be documented in writing. Any protocol amendment must be approved and signed by the Sponsor and the Principal Investigator. It should be submitted to the appropriate REC for information and approval, in accordance with local requirements, and to regulatory agencies if required. Approval by REC (and the Regulatory Authority, if applicable) must be received 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 the Sponsor or the Principal Investigator.

The Investigator will provide in writing the reasons for the proposed amendment and will discuss with the Sponsor.

The standard text in the ICF 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 REC for the trial. However, if the SRG decide to reduce the planned dose, HMR consider it essential to fully inform the subject why; a reduction in dose might be due to poor tolerability; and that might affect the subject's decision to remain in the trial. HMR will obtain prior approval from the REC for the information update 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 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 REC, or drug safety problems.

Both the Sponsor and the Investigator reserve the right to terminate the study at any time before inclusion of the intended number of subjects, but intend to exercise this right only for valid scientific or administrative reasons. Should early termination 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 interests.

Reasons for early termination by the Sponsor(s) may include but not be limited to:

- Enrolment rate is too low
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the test article
- Suspected lack of efficacy of the test article
- Following the recommendation of the Safety Review Committee or the 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 terminated early, either by the Sponsor or by the Investigator, the Investigator must:

- Complete all CRFs to the fullest possible extent
- Return all test articles, CRFs, and related study materials to the Sponsor
- Answer all questions from the Sponsors or their representatives related to subject data collected before the termination of the study
- Ensure that subjects enrolled in the study who had not yet reached the Follow-up and long-term Follow-up Visits are followed up with the necessary medical care.
- Provide in writing the reasons for the decision to the national health authority and the Sponsor.

15. Ethics

The experimental protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki and ICH guidelines for Good Clinical Practice (International Committee for Harmonization; addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)). DNDi assures that it will comply with all applicable state, local and foreign laws for protecting the rights and welfare of human subjects. This protocol and any protocol amendments will be reviewed / approved by an REC before its implementation.

It is the responsibility of the Global or National Coordinating Investigator/Investigator to apply for review to the REC of the country where the study takes place regarding local rules and regulations. Written approval from all involved RECs must be obtained before implementation of any protocol-specified intervention or investigation

provided to the subject (such as subject information sheets or descriptions of the study).

Any modifications made to the protocol after receipt of the REC approval must also be submitted by the Investigator in writing to the REC in accordance with local procedures and regulatory requirements.

All subjects must give written consent to participate in this trial. Consent for screening evaluations may be obtained using the generic ICF for the HMR healthy volunteer panel that has been approved by London – Brent Research Ethics Committee and subsequently by the Generic Document Review Committee (GDRC). The trial-specific ICF 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 dose 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.

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 GDRC. 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 REC are informed promptly of SUSARs (see Section 8.6.5), 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 REC, if applicable. The Sponsor will provide the Investigator, the REC and the MHRA with annual Development Safety Update Reports (DSURs) of each IMP under investigation. 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 REC of any SAE that occurs during this trial (see Section 8.6.5). The Investigator will provide the REC with annual progress reports of the trial, if the trial lasts longer than a year.

The Investigator will report to the REC any protocol deviation that is, in his opinion, of clinical significance. The Investigator will also inform the REC 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 REC 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 REC and the MHRA are notified that the trial has finished. 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 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 REC 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. Compensation of volunteers

The Sponsor agrees to abide by the Association of the British Pharmaceutical Industry Guidelines for medical experiments in healthy human volunteers (Guidelines for Phase 1 Clinical Trials, 2012 edition) 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.

15.3. Insurance and Liability

DNDi is insured to indemnify the Investigator against any claim for damages brought by a subject who suffers from a research related injury during the performance of the trial according to the protocol, except for claims that arise from malpractice and/or negligence.

In accordance with local regulations, DNDi will contract insurance for all study participants.

15.4. 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.

15.5. 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.

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.

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Appendices

Changes introduced in protocol version