DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL

A Phase 1, Randomized, Open-Label, Parallel-Group, Relative Bioavailability Study to Investigate the Pharmacokinetics, including Food Effect, as well as the Safety and Tolerability of Single Doses of New Immediate Release Tablet Formulations of Emodepside (BAY 44-4400), compared to Oral Solution, in Healthy Male Subjects

Short title	Relative Bioavailability Study of Emodepside IR-tablets and Solution
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-03
EudraCT	2017-003091-31
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Clinical Trial Protocol Version / Date	Version 3, 01 February 2018
Protocol Amendment Number / Date	N/A

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CLINICAL TRIAL PROTOCOL SIGNATURE PAGE

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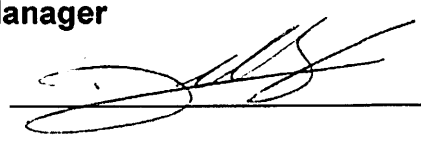
Signature  1 Feb 2018
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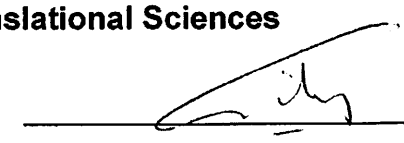
Signature  01 February 2018
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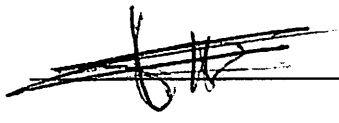
Signature  01 Feb 2018
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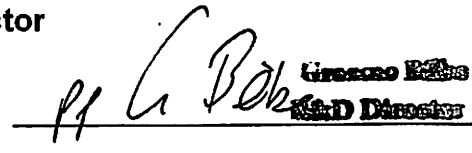
Signature  1-2-18
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Investigators Signature Page

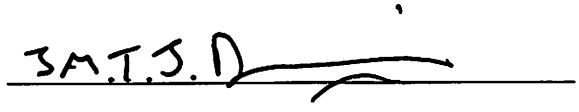
I have read this protocol and agree that it contains all necessary details for carrying out this trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.

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 fulfil 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  02 FEB 2018
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ABBREVIATIONS – GLOSSARY OF TERMS

ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
ANOVA	Analysis of variance
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 in die (twice-daily)
BMI	Body Mass Index
BP	Blood Pressure
CBC	Complete Blood Count
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatinine Kinase
CL	Clearance
C_{max}	Maximum observed concentration
CRF	Case Report Form
CRO	Contract Research Organization
CV	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4
DNDi	Drugs for Neglected Diseases initiative
ECG	Electrocardiogram
IC20	Inhibitory Concentration 20
ICF	Information Consent Form
IMP	Investigational Medicinal Product
IR	Immediate Release
F	Female
FDA	Food and Drug Administration
FIH	First-In-Human
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice
GDRC	Generic Documents Review Committee
GGT	Gamma-Glutamyl Transpeptidase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HDL	High Density Lipoprotein
hERG	Human ether-a-go-go-related gene

HIV	Human Immunodeficiency Virus
HMR	Hammersmith Medicines Research
HR	Heart Rate
ICF	Information and Consent Form
ICH	International Conference on Harmonization
IR	Immediate Release
IRB	Institutional Review Board
LDH	Low Density Lipoprotein
LF	Lymphatic filariasis
LS-means	Least Squares Means
LSF	Liquid Service Formulation
M	Male
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MDA	Mass Drug Administration
MedDRA	Medical Dictionary For Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MIC	Minimum Inhibitory Concentration
mL	Millilitre
MRT	Mean Residence Time
MTT	4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide
NOAEL	No Observed Adverse Effect Level
ng	Nanogram
OCP	Onchocerciasis Control Programme
OD	Omnie die (once-daily)
P-gp	P-glycoprotein
PK	Pharmacokinetics
p.o	Per Os (To Be Taken By Mouth)
ppm	Parts Per Million
PT	Prothrombin Time
RBC	Red Blood Cell
REC	Research Ethics Committee
QTcB	QT Corrected By Bazett’s Formula
QTcF	QT Correct By Fridericia's Formula
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SRG	Safety Review Group
SUSAR	Serious Unexpected Adverse Event
T_{max}	Time of Maximum Observed Concentration
TEAE	Treatment Emergent Adverse Event

TSH	Thyroid-Stimulating Hormone
ULN	Upper Limit Of Normal
UV	Ultraviolet
WBC	White Blood Cell
WHO	World Health Organization
WHO DD	World Health Organisation Drug Dictionary

PROTOCOL SUMMARY

Trial Objectives	**Primary Objective** • To investigate the pharmacokinetics, including relative bioavailability and food effect, of two new immediate release (IR)-tablet formulations of emodepside in comparison to the liquid service formulation (LSF) oral solution. **Secondary Objectives** • To investigate and compare safety and tolerability of single oral doses of emodepside formulations in healthy subjects.
Trial Endpoints	**Primary Endpoint** • Based on the plasma concentration–time data, the following PK parameters of emodepside will be calculated: ○ Main: $AUC_{0\text{-}7d}$, $AUC_{0\text{-}7d}$/Dose, C_{max}, C_{max}/Dose **Secondary Endpoints** • Safety and Tolerability Variables: ○ Adverse Events (AEs) ○ Physical and neurological examination findings ○ Vital signs (BP and HR), ○ 12-lead ECG (HR, PR, QRS, QTcB, QTcF), will be analysed *ad hoc* for safety and for the final data base and report by central reading ○ 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); ▪ Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT); ▪ Biochemistry: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), amylase, lipase, glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium; ▪ Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites and microscopy (reflex). **Other and exploratory endpoints** • Pharmacokinetic: ○ $AUC_{0\text{-}7d,norm}$, $C_{max,norm}$, $t_{1/2,0\text{-}24h}$, $t_{1/2,0\text{-}7d}$, t_{max}, MRT, points terminal
Trial Design	The study will be done in 2 parts, as follows: • Part 1 – single oral doses of 5 mg emodepside will be tested: ○ Part 1a – the LSF (reference formulation) and 2 new IR-tablet formulations (test formulations) will be administered in the fasted state.

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

Part 1b – the 2 new IR-tablet formulations will be administered in the fed state (high-fat, high-calorie meal).

Part 2 – single oral doses of 10 mg emodepside will be tested: depending on the results from Part 1, one or both IR-tablet formulations will be administered in the fasted state.

The treatments in each study part are as follows:
<table>
<tr><th>Part</th><th>Treatment</th><th>Formulation, dose and condition</th><th>Number of subjects</th></tr>
<tr><td>Part 1a</td><td>A</td><td>5 mg emodepside LSF, fasted</td><td>12</td></tr>
<tr><td></td><td>B</td><td>5 mg emodepside IR-tablet #406, fasted</td><td>12</td></tr>
<tr><td></td><td>C</td><td>5 mg emodepside IR-tablet #416, fasted</td><td>12</td></tr>
<tr><td>Part 1b</td><td>D</td><td>5 mg emodepside IR-tablet #406, fed</td><td>12</td></tr>
<tr><td></td><td>E</td><td>5 mg emodepside IR-tablet #416, fed</td><td>12</td></tr>
<tr><td>Part 2</td><td>F*</td><td>2 x 5 mg emodepside IR-tablet #406, fasted</td><td>12</td></tr>
<tr><td></td><td>G*</td><td>2 x 5 mg emodepside IR-tablet #416, fasted</td><td>12</td></tr>
</table>
* one or both treatments may be tested, depending on results from Part 1

Up to 84 healthy volunteers will be enrolled, in up to 7 treatment arms made up of 12 subjects each.
</td></tr>
<tr><td>Main Entry Criteria</td><td>
Inclusion:

Male, Caucasian volunteers, deemed healthy based on a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine.
18 to 45 years of age
Normal body weight (Body Mass Index (BMI); Quetelet index) in the range 18.0 to 30.1 kg/m^2 at screening
Mean blood pressure and heart rate (from the triplicate readings) in the supine position at the screening assessment within the following ranges:

90–140 mm Hg systolic BP
60–90 mm Hg diastolic BP
45–100 beats/min HR

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

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

	Overvolunteering Prevention System (TOPS) 8. Willingness to follow contraception requirements of the study, from the first dose of the IMP until 90 days after dosing and inform HMR as soon as possible if their partner becomes pregnant in the 90 days after dosing **Exclusion:** 9. 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 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 (e.g. stomach bypass) or medical condition that might affect absorption of the study drug when taken orally 12. 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 13. Loss of more than 400 mL of blood within the 3 months before admission 14. Clinically relevant history of vital organ disease, or other organ or central nervous system disease (e.g. diabetes mellitus, liver disease, seizures, etc.) 15. Current or previous medical or psychiatric disorder that, in the opinion of the Investigator or the Sponsor, would increase the risk and ability to participate in and/or complete the study 16. Positive test for hepatitis B, hepatitis C or HIV 17. Febrile illness (e.g. fever) within 1 week before the first dose of study medication 18. History of a severe allergy, non-allergic drug reaction, severe adverse reaction to any drug, or multiple drug allergies 19. 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 year, or intake of more than 21 units (1 unit = ½ pint of beer, 1 small glass of wine or 1 measure of spirits) of alcohol weekly 21. Regular daily consumption of more than one litre of beverages containing xanthine 22. Daily consumption of more than 10 cigarettes or more than 6 grams (1/4 ounce) of tobacco 23. Use of a prescription medicine during the 28 days before the dose of study medication, or use of an over-the-counter medicine (with exception of acetaminophen (paracetamol)), during the 7 days before the dose of study

	medication 24. Use, within 14 days before the dose of study medication, 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 (see list in the Study Procedures Manual) 25. Use, within 14 days before the dose of study medication, of dietary supplements or herbal remedies that are known to be strong inhibitors of P-gp, or other co-medications known to be relevant substrates of P-gp (see list in the Study Procedures Manual) 26. Relevant pathological abnormalities in the ECG at screening, such as: • second or third-degree atrioventricular (AV) block • prolongation of the QRS complex > 120 msec, • QTc-interval (QTcB or QTcF) > 450 msec. The mean of the triplicate ECG readings will be used to assess eligibility. 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 during 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
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 at the discretion of the Investigator upon consultation with the Sponsor.
Study Duration	• Each subject's participation in the study will last for up to 5 weeks, and will include a Screening visit (within 4 weeks before dosing), a 5-day in-house evaluation period (Day –1 to Day 3), followed by an outpatient visits (on Days 5), and a final Follow-up visit (on Day 7). • Overall, including the recruitment period, the trial is expected to last approximately 6 months
Study treatments	Emodepside oral LSF will be provided as 0.1% (w/v) 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. Each bulk solution bottle contains 20 mg emodepside, corresponding to 20

	mL solution. 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 will be used for application of doses of 5 mg, corresponding to application of 5 mL of the solution. The solution is composed of the active substance emodepside and excipients. Detailed information on the drug substance emodepside (BAY 44–4400) is given in the Investigator's Brochure. Emodepside tablet #406 contains granules of emodepside and the polymer hypromellose acetate succinate as a solid dispersion to enhance solubility. Tablets contain 5 mg active substance (emodepside), and excipients: Emodepside tablet #416 contains granules of emodepside and the polymer copovidone as a solid dispersion to enhance solubility. Tablets contain 5 mg active substance (emodepside) and excipients.
Sample Size	No formal statistical sample size estimation has been performed, due to the exploratory nature of this study. 10 subjects per treatment arm is considered sufficient to examine the safety and tolerability of emodepside, as well as the PK after single doses. However, 12 subjects will be recruited and enrolled per treatment arm to ensure a minimum of 10 evaluable subjects complete the study.
Statistics	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 PK sample has been analysed. • PK Parameter Population: All subjects in the PK Concentration Population for whom PK 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. 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 mean23; 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 will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically. To assess the relative bioavailability, analysis of variance (ANOVA) models will be fitted to the tablet (test) and solution (reference) data with the logarithm of the pharmacokinetic parameters AUC0-7d/Dose or Cmax/Dose as the dependent variable, and formulation as a fixed effect. The point estimates least squares (LS)-means and 90% confidence intervals for the ratios “B / A” and “C / A” will be calculated in Part 1a. In Part 2, “F/A” and/or “G/A” will be calculated. The acceptance range 80 – 125% will be applied for these assessments. To assess the effect of food, ANOVA models will be fitted to the data with the logarithm of the pharmacokinetic parameters AUC0-7d/Dose or Cmax/Dose as the dependent variable, and fed (test) or fasted (reference) as a fixed effect. In Part 1, the point estimates and 90% confidence intervals for the ratios “D/B” and “E/C” will be calculated. The acceptance range 80 – 125% will be applied for the assessment of a potential food effect. To assess dose proportionality, for each tablet type, exploratory ANOVA models will be fitted to the relevant fasted data in Parts 1 and 2 with the logarithm of the pharmacokinetic parameters AUC0-7d or Cmax as the dependent variable and dose as a fixed effect. The ratios “F/B” and/or “G/C” will be calculated.

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[1,2].

An estimated 18 million people suffer from onchocerciasis[3], with 99% of cases in 31 African countries, and 187 million at risk in 2015[4]. Although the disease is almost exclusively confined to Africa, some foci still exist in Yemen and South America (Brazil and Venezuela)[5].

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 and can even induce premature child weaning by affected mothers.

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[6] that 746,000 patients are visually impaired, 265,000 are blinded and more than 4 million suffer from severe itching due to onchocerciasis[7].

The burden associated with onchocerciasis is estimated at more than 1 million disability-adjusted life years (DALYs) in 2013 worldwide[8].

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[9] 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[10] 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[11] to African Control programs in 24 African countries under the direction of APOC/ WHO until 2015[12].

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 drug is therefore needed to kill the adult worm, stop the perpetual 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 disease that occurs exclusively in West and Central Africa; an estimated 13 million people are infected with *Loa loa*[13]. 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[14]. 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[15].

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[13,16].

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 is a relative bioavailability study to investigate the safety, tolerability, food effect and pharmacokinetics of emodepside (BAY44-4400) new immediately-release tablet formulations, compared to oral solution, after a single dose 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*[17,18].

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[19]. 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)[20].

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 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 (PK). The preliminary results are favourable, and 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 relative bioavailability study, PK as well as safety and tolerability, and food effect of single doses of 2 new immediate release (IR)-tablet formulations of emodepside will be compared to the oral liquid service formulation (LSF) used in the FIH study.

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 i.e., 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 (NOEL) 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 NOAEL 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 electrocardiogram (ECG) results in anesthetized dogs. However, a moderate vasodilatation (reduction of total resistance, slight decrease of arterial blood pressure (BP), 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 BP or heart rate (HR) 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 (P-gp) mediated. Therefore, a role for P-gp in the PK 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 $AUC_{0\text{-}24h}$ 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/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 sufficient to support this phase I study in human subjects.

1.4. Summary of human clinical data

Results of the first in man single dose escalation study (ref. DNDI-EMO-001)

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 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 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)**
Gastro-intestinal 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 TEAEs 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 TEAEs 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 treatment-related eye disorders TEAEs were of mild intensity, resolved spontaneously (without treatment), and were more frequently reported with highest dose (40 mg). Among them, the TEAEs 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 with regards to treatment 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 post-administration. 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 post-administration (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 preliminary results suggest an increase of blood glucose and insulin, 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 in subjects exposed to treatment, regardless of the formulation.

Preliminary 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 single doses of emodepside have been administered to humans and were well tolerated. Based on the FIH single ascending dose clinical study, overall tolerability to emodepside has been acceptable up to 20 mg of LSF formulation. 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.
- Pre-clinical data suggests that plasma exposure following emodepside as IR-tablets is not high than the one observed after LSF administration at the same dose.
- In Part 1 of this study, single doses of 5 mg emodepside will be administered in the fed and fasted states. Based on PK data from the FIH study, exposure to emodepside following administration of the IR-tablet in the fed state is likely to be similar to or lower than the IR-tablet administered in the fasted state. Therefore, it is acceptable to test the fed and fasted doses in parallel or sequentially in Part 1.
- Part 2 of this study, in which single doses of 10 mg emodepside will be tested, will proceed only if the PK, safety and tolerability after single doses of 5 mg emodepside in Part 1 are acceptable, and provided the Investigator and Sponsor's Medical Monitor agree that it is appropriate to give a higher dose. The total dose of emodepside for any subject will not exceed 10 mg.

2. Study Objectives and Endpoints

2.1. Objectives

2.1.1. Primary Objective

- To investigate the pharmacokinetics, including relative bioavailability and food effect, of two new immediate release (IR)-tablet formulations of emodepside in comparison to the liquid service formulation (LSF) oral solution.

2.1.2. Secondary Objectives

- To investigate and compare safety and tolerability of single oral doses of emodepside formulations in healthy subjects.

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Based on the plasma concentration–time data, the following PK parameters of emodepside will be calculated:
  - Main: $AUC_{0\text{-}7d}$, $AUC_{0\text{-}7d}$/Dose, C_{max}, C_{max}/Dose

2.2.2. Secondary Endpoints

- Safety and Tolerability Variables:
  - Adverse Events (AEs)
  - Physical and neurological examination findings
  - Vital signs (BP and HR),
  - 12-lead ECG (HR, PR, QRS, QTcB, QTcF), will be analysed *ad hoc* for safety and for the final data base and report by central reading
  - 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);
    - Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT);
    - Biochemistry: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), amylase, lipase, glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium;
- Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites and microscopy (reflex).

2.2.3. Other and exploratory endpoints

- Pharmacokinetic:
  - $AUC_{0\text{-}7d,norm}$, $C_{max,norm}$, $t_{1/2,0\text{-}24h}$, $t_{1/2,0\text{-}7d}$, t_{max}, MRT, points terminal

3. Study design and study design rationale

3.1. Study design

This is a single-centre, open-label, randomized, parallel-group relative bioavailability study in healthy men. The study will be done in 2 parts, as follows:

- Part 1 – single oral doses of 5 mg emodepside will be tested:
  - Part 1a – the LSF (reference formulation) and 2 new IR-tablet formulations (test formulations) will be administered in the fasted state.
  - Part 1b – the 2 new IR-tablet formulations will be administered in the fed state (high-fat, high-calorie meal).
- Part 2 – single oral doses of 10 mg emodepside will be tested: depending on the results from Part 1, one or both IR-tablet formulations will be administered in the fasted state.

The treatments in each study part are summarised in Table 1.

Table 1. Planned treatments by dose, formulation and condition

Part	Treatment	Formulation, dose and condition	Number of subjects
Part 1a	A	5 mg emodepside LSF, fasted	12
	B	5 mg emodepside IR-tablet #406, fasted	12
	C	5 mg emodepside IR-tablet #416, fasted	12
Part 1b	D	5 mg emodepside IR-tablet #406, fed	12
	E	5 mg emodepside IR-tablet #416, fed	12
Part 2	F*	2 x 5 mg emodepside IR-tablet #406, fasted	12
	G*	2 x 5 mg emodepside IR-tablet #416, fasted	12

* one or both treatments may be tested, depending on results from Part 1

Up to 84 healthy volunteers will be enrolled, in up to 7 treatment arms made up of 12 subjects each.

The 36 subjects in Part 1a will be randomised to one of 3 treatments (A, B or C). The 24 subjects in Part 1b will be randomised to one of 2 treatments (D or E). Parts 1a and 1b may proceed in parallel, or may be done sequentially.

After at least 10 subjects have received each treatment in Part 1, and data up to 72 h after dosing are available, there will be a Dose Decision Meeting to determine which treatment(s) will be tested in Part 2 (see section 7.5).

In Part 2, either treatment F, G or both F and G will be tested. There will be 12 subjects enrolled for each treatment tested. If both treatments are tested, they will be done in parallel, and subjects will be randomised to one of the 2 treatments.

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

3.2. Study duration and duration of subject participation

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

Eligible subjects will be admitted to the ward on the afternoon of Day –1 (the day before dosing). They will remain on the ward until the morning of Day 3 (4 nights and 5 days in a row); during that time, they will receive a single oral dose of emodepside.

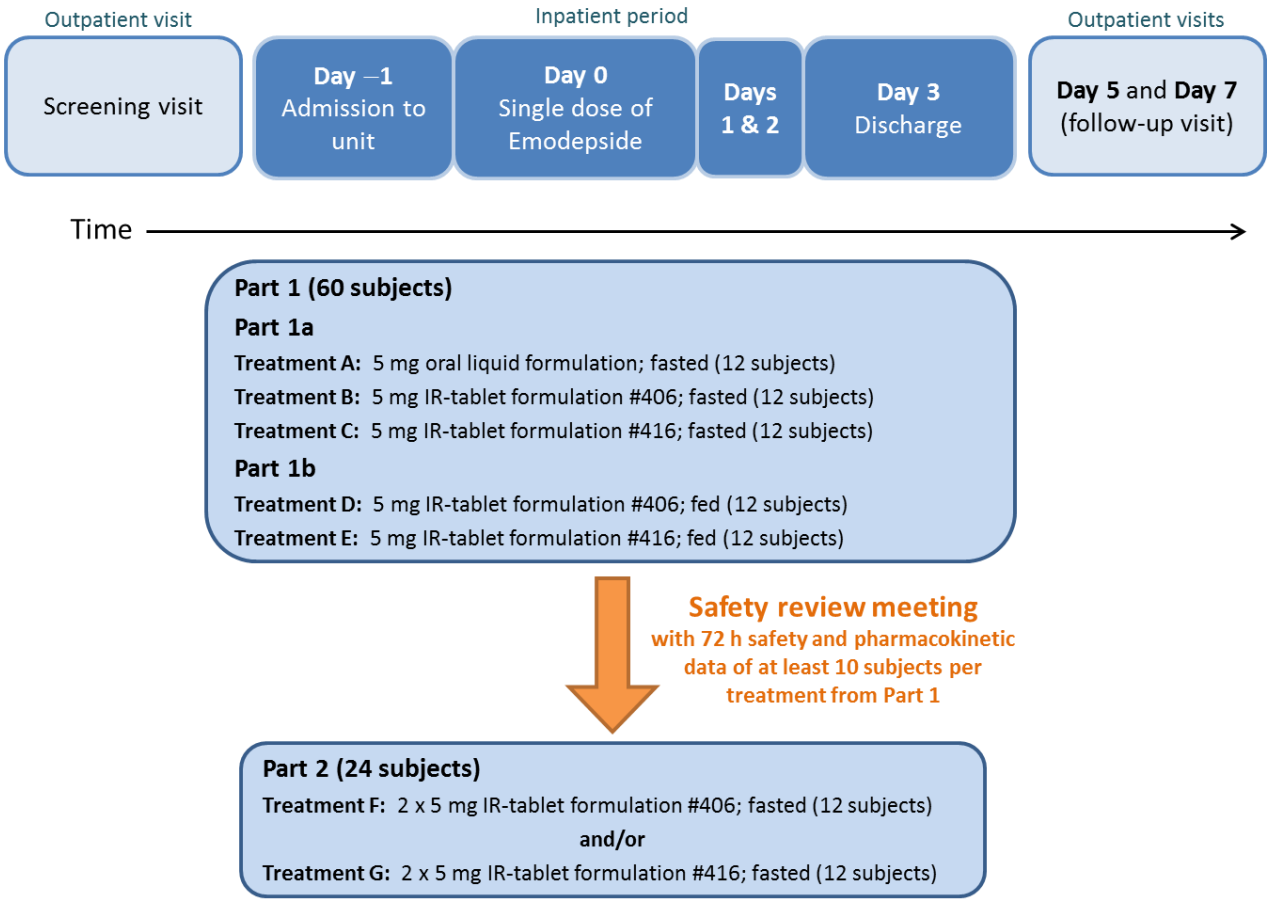
Safety, tolerability, and PK assessments will be done before and regularly after dosing. Each subject will undergo a full day of assessments (including PK) on the day of dosing (Day 0).

Subjects will be discharged from the study unit on Day 3, provided there are no medical objections. Subjects will attend the ward for outpatient (ambulatory) visit on Day 5 and a final Follow-up visit on Day 7, at 1 week after their dose of emodepside.

The study design is summarised schematically in Figure 1.

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

Figure 1 – Overall study design



3.3. Definition of the end of trial

The end of the trial is defined as the final Follow-up visit by the last subject (or final contact with the subject, if that is later).

If the trial is terminated early, the trial ends when the Sponsor notifies the Investigator in writing that the trial has finished, or when the last subject attends the final Follow-up visit, whichever is later.

3.4. Rationale of study design

The study will be performed in a randomized, open-label, parallel group design.

The open design of the trial has the important disadvantage that both investigator and subjects are aware that active treatment is being given, and there is no placebo. The possibility of bias must therefore be taken into account in the assessment of AEs in particular. However, the primary objective of the study is to compare the PK of emodepside after different formulations, which will be assessed using an objective test measured by an external laboratory. Relative bioavailability and food effect form part of the PK assessment. Most of the other assessments are also objective, either because they are measured by a laboratory or are measured using automated means (HR, BP, and ECG).

After a single dose, emodepside is rapidly absorbed and peak plasma concentrations occur within a few hours after dosing. There is a short half-life in the first 24 h

(distribution/elimination phase) followed by a long terminal elimination half-life ($t_{1/2}$ >500 h). Crossover designs are attractive because they can enhance the power of a trial to distinguish between treatments; that is because within-subject variability is generally less than between-subject variability. However, crossover designs are subject to carryover of effects from one treatment to the next, especially if the elimination half-life is long. Because of this, a parallel group design was chosen for this study and PK samples will be taken at the Follow-up Visit (168 h after dosing). Treatments in Part 1 will be randomized to reduce the likelihood of period or seasonal effects confounding the study assessments. Part 2 will also be randomized if both treatments are tested.

The study will be performed in healthy male Caucasian volunteers, in order to avoid ethic and sex differences that may increase pharmacokinetic variability.

In the FIH study, single doses of 5 and 10 mg emodepside, administered as LSF oral solution in the fasted state, were safe and well tolerated. Since those doses are likely to fall within the dose range tested in later phase studies, and have previously been well tolerated in healthy volunteers, they have been selected for this relative bioavailability study. It is anticipated that emodepside exposure following IR-tablets (in both fasted and fed states) will be no higher than exposure following the same dose of LSF oral solution. Anticipated exposures for each formulation tested in this study are provided below.

Following a single dose of 5 mg emodepside, administered as LSF oral solution in the FIH study, mean ± SD (CV%) C_{max} was 93.2 ± 15.7 ng/mL (16.8%) and AUC_{last} was 1736.2 ± 392.5 ng*h/mL (22.6%). Exposures in Part 1 of this study are likely to be similar to, or lower than, these values.

Following a single dose of 10 mg emodepside, administered as LSF oral solution in the FIH study, mean ± SD (CV%) C_{max} was 178.6 ± 47.9 ng/mL (26.8%) and AUC_{last} was 3165.2 ± 817.2 ng*h/mL (25.8%). Exposures in Part 2 of this study are likely to be similar to, or lower than, these values.

The highest single dose which has been shown to be well tolerated is 20 mg LSF oral solution, which resulted in mean ± SD (CV%) C_{max} of 315.7 ± 87.6 ng/mL (27.7%) and AUC_{last} of 7617.0 ± 1467.7 ng*h/mL (19.3%). Even if exposures in Parts 1 and 2 are higher than anticipated, they are unlikely to exceed these values.

Therefore, the proposed doses to be tested in this study are considered acceptable.

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 DNDi Medical Monitor before the 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. Mean blood pressure and heart rate (from the triplicate readings) in the supine position at the screening assessment within the following ranges:
    a. 90–140 mm Hg systolic BP
    b. 60–90 mm Hg diastolic BP
    c. 45–100 beats/min HR
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 follow contraception requirements of the study, from the first dose of the IMP until 90 days after dosing and inform HMR as soon as possible if partner becomes pregnant in the 90 days after dosing.

4.2. Exclusion criteria

The presence of 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 (e.g. 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 (e.g. diabetes mellitus, liver disease, seizures, etc.)

7. Current or previous medical or psychiatric disorder 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 (e.g. 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 years, or intake of more than 21 units (1 unit = ½ pint of beer, 1 small glass of wine or 1 measure of spirits) of alcohol weekly
13. Regular daily consumption of more than one litre of beverages containing xanthine
14. Daily consumption of more than 10 cigarettes or more than 6 grams (1/4 ounce) of tobacco
15. Use of a prescription medicine during the 28 days before the dose of study medication, or use of an over-the-counter medicine (with exception of acetaminophen (paracetamol)), during the 7 days before the dose of study medication
16. Use, within 14 days before the dose of study medication, 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 (see list in the Study Procedures Manual)
17. Use, within 14 days before the dose of study medication, of dietary supplements or herbal remedies that are known to be strong inhibitors of P-gp, or other co-medications known to be relevant substrates of P-gp (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
    - prolongation of the QRS complex > 120 msec,
    - QTc-interval (QTcB or QTcF) > 450 msec.

    The mean of the triplicate ECG readings will be used to assess eligibility.
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

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 from 24 h before Screening, and from 24 h before admission until after the Follow-up visit.

No strenuous exercise will be allowed from 48 h before Screening until after the Follow-up visit.

Subjects should fast (no food or drink, except water) for at least 10 h before Screening.

On Day 0, subjects in Part 1a and Part 2 will fast (no food or drink, except water) overnight for at least 10 h before dosing, until at least 4 h after dosing. Subjects in Part 1b will fast (no food or drink, except water) overnight until approximately 30 min before dosing, at which time they will be given a standard Food and Drug Administration high-calorie, high-fat breakfast consisting of: 2 fried eggs, 2 strips of bacon, 2 slices of toast and butter, 4 ounces of hash brown potatoes, and a glass of whole milk. They must finish the breakfast at least 5 min before dosing.

For all subjects, post-dose mealtimes on Day 0 will be as follows:

- Lunch: approximately 5 h after dosing
- Snack: approximately 8 h after dosing
- Dinner: approximately 12 h after dosing

The content of meals on Day 0 will be standardised: the content of lunch, snack and dinner will be the same for each subject.

On all other study days on which subjects are resident, 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.

From the first dose until 90 days after the dose, subjects must not have sex without using a condom, unless they have had a vasectomy or their partner is not of childbearing potential.

5. Schedule of assessments

Procedure	Screening	Inpatient																		Follow-up	
	Day –28 to –2	Day –1	Day 0													Day 1		Day 2	Day 3	Day 5	Day 7
		hours	*–1*	*0*	*0.25*	*0.5*	*1*	*1.5*	*2*	*2.5*	*3*	*4*	*6*	*8*	*12*	*24*	*36*	*48*	*72*	*120*	*168*
Subject demographics and informed consent	X																				
Inclusion/exclusion criteria - Eligibility check	X	X																			
Medical history/prior medication	X																				
Inpatient stay		←																	→		
Administration of emodepside[1]				X																	
Outpatient visit	X																			X	X
Drugs of abuse screen	X	X																			
Alcohol breath test	X	X																			
Physical and neurological examination[2]	X	X							X							X	X	X	X	X	X
Vital signs[3]	X		X			X	X	X	X		X	X		X	X	X	X	X	X	X	X
12-lead safety ECG[4]	X		X			X	X	X	X		X	X		X	X	X		X	X	X	X
Laboratory safety tests[5,6]	X		X													X		X	X	X	X
Serology[7]	X																				
Blood samples for assay of emodepside[6]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE questioning[8]	←																			→	

1. Subjects in Part 1a and Part 2 will fast for 10 h before until at least 4 h after dosing. Subjects in Part 1b will be given a high-calorie, high-fat breakfast approximately 30 min before dosing, which they must finish at least 5 min before dosing. Standard meals will be served at approximately 5 h (lunch), 8 h (snack) and 12 h (dinner) after dosing on Day 0. Procedures scheduled at the same time as a meal will be completed before the meal.
2. A full physical examination will be done at Screening and Follow-up. A brief (symptom-directed) physical examination and short neurological examination will be undertaken at all other time points. Any abnormalities will trigger a full neurological examination and/or opening of an AE as appropriate. Height, weight and body mass index (BMI) will be assessed at screening, and weight will be assessed on Day –1.
3. Vital signs will comprise supine blood pressure and heart rate. Subjects should rest in the supine position for at least 10 min before vital signs measurements. Vital signs will be measured in triplicate at screening and pre-dose (–1 h); single measurements at all other time points. Body temperature will be measured on day -1.
4. Subjects should rest in the supine position for 10 min before ECG measurements. Measurement in triplicate at screening and pre-dose (–1 h); single measurements all other time points.

5. Blood and urine samples for clinical laboratory safety tests (haematology, biochemistry, coagulation and urinalysis).
6. Subjects should rest in the supine position for 10 minutes before blood is drawn (if possible).
7. Serology tests will comprise HIV 1 & 2 and hepatitis B & C.
8. Adverse event monitoring will be done throughout the study, but scheduled questioning will be done at the time points of scheduled blood draws.

6. Enrolment procedures

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

Hammersmith Medicines Research Limited (HMR),
Cumberland Avenue, Park Royal
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 'Enrolled' – i.e., received treatment) or reason for not enrolling (Screen Failure) or not being randomised, whenever applicable.

Screening should occur between 2 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 16.1 for Informed Consent Procedures) to participate in this trial. Consent for screening evaluations may be obtained using the Information and Consent Form (ICF) for the HMR healthy volunteer panel (see Section 16).

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 dose ('Enrolled' subjects). Subject numbers in the trial will be as shown in Table 2. In Part 1 only, subject numbers will be allocated to treatment according to a randomization schedule prepared by an independent HMR statistician, using a SAS program. Sufficient subjects will be screened to ensure 12 subjects are enrolled per treatment arm tested.

7. Study treatments

7.1. Doses and treatment regimens

The study will be done in 2 parts. In Part 1, each subject will receive a single oral dose of 5 mg emodepside in the fasted state (Part 1a) or in the fed state (Part 1b). In Part 2, each subject will receive a single oral dose of 10 mg emodepside in the fasted state.

In Part 1, two new IR-tablet formulations of emodepside (#406 and #416) will be compared to LSF solution (concentration 1 mg/mL). In Part 2, one or both IR-tablet formulations from Part 1 will be tested.

Each subject will receive a single dose of emodepside. The treatments in each study part will be as follows.

- Part 1a:
  - Treatment A: 5 mg emodepside LSF, fasted
  - Treatment B: 5 mg emodepside IR-tablet #406, fasted
  - Treatment C: 5 mg emodepside IR-tablet #416, fasted
- Part 1b:

- Treatment D: 5 mg emodepside IR-tablet #406, fed
- Treatment E: 5 mg emodepside IR-tablet #416, fed

- Part 2:
  - Treatment F: 2 x 5 mg emodepside IR-tablet #406, fasted
  - Treatment G: 2 x 5 mg emodepside IR-tablet #416, fasted

In Part 1a, subjects will be randomized 1:1:1 to receive Treatment A, B or C. In Part 1b, subjects will be randomized 1:1 to receive Treatment D or E. Depending on the results from Part 1, all subjects in Part 2 may receive Treatment F, all subjects may receive Treatment G, or half of the subjects may receive each treatment. If one treatment is tested, 12 subjects will be allocated to that treatment. If both treatments are tested subjects will be randomized 1:1 to receive Treatment F or G. Enrolled subjects will be given a unique ID (subject number; Table 2) 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 2. Study treatment and subject numbers by study part

Part	Treatment	Number of subjects	Subject numbers
Part 1a	A, B or C	36 (12 per treatment)	1001–1036
Part 1b	D or E	24 (12 per treatment)	2001–2024
Part 2	F or G*	24 (12 per treatment)	3001–3024

* one or both treatments may be tested, depending on results from Part 1. If only one treatment is selected, the first 12 subject numbers will be used.

Replacements for withdrawn subjects will be given a number equal to that of the subject that they replaced plus 100 (e.g. Subject 1036 would be replaced by Subject 1136).

7.2. Emodepside Liquid Service Formulation

Emodepside oral LSF will be provided as 0.1% (w/v) 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.

Each bulk solution bottle contains 20 mg emodepside, corresponding to 20 mL solution. 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 will be used for application of doses of 5 mg, corresponding to application of 5 mL of the solution.

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

- macrogol 400
- polysorbate 20
- levomenthol
- butylhydroxyanisole

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

7.3. Emodepside Immediate Release Tablets

Both emodepside tablets are IR forms with rapid dissolution *in vitro*. Both tablet formulations are expected to disintegrate in the acid milieu of the stomach and the resultant granules to dissolve rapidly in the upper intestine.

Emodepside tablet #406 contains granules of emodepside and the polymer hypromellose acetate succinate as a solid dispersion to enhance solubility. Tablets contain 5 mg active substance (emodepside), and the following excipients:

- hypromellose acetate succinate
- macrogol 15 hydroxystearate
- croscarmellose sodium
- microcrystalline cellulose
- magnesium stearate

Emodepside tablet #416 contains granules of emodepside and the polymer copovidone as a solid dispersion to enhance solubility. Tablets contain 5 mg active substance (emodepside) and the following excipients:

- copovidone
- macrogol 15 hydroxystearate
- croscarmellose sodium
- microcrystalline cellulose
- magnesium stearate

Both tablets are film-coated with a coating composed of hypromellose, macrogol, ferric oxide red, and titanium dioxide. They are identical in appearance: they are both round, pink, tablets with a diameter of 5 mm. Bulk tablets are packaged in HDPE bottles with a desiccant capsule inside each bottle and the bottles are closed with child-resistant polypropylene screw cap closures with induction seal.

Subjects will be instructed to swallow the IR-tablets whole, without chewing the medication prior to swallowing.

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

7.4. IMP supply and handling

Formulation and Supplier:

Emodepside will be supplied by the Sponsor, DNDi, as emodepside LSF solution and IR-tablets (#406 and #416).

The Sponsor will supply the bulk study drug to the study site. 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 and IR-tablets will be dispensed in the Phase 1 Unit into individual dosing containers by 2 appropriately qualified members of the pharmacy team. Instructions provided in the Pharmacy Manual/Study Procedures Manual must also be followed.

7.5. Dose decision

The decision to go ahead with one or both treatments in Part 2 will be made based on the safety, tolerability and PK of the treatments in Part 1.

The dose decision will be made by the Safety Review Group (SRG) at the Safety Review Meeting. The treatments will not be decided until the SRG has reviewed the safety, tolerability and PK data of at least 10 subjects per treatment. Safety, tolerability and PK data up to a minimum of 72 h post-dose should be reviewed before a decision can be made.

The treatments in Part 2 will be tested only if the Investigator and Sponsor's medical representative agree that it is appropriate to give the higher dose.

7.6. 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 AEs, 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 Medicines and Healthcare products Regulatory Agency (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 Reference 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 CRF.

7.9. Storage

Emodepside oral LSF solution should be stored at 2°C – 8°C in the original container (upright storage).

Emodepside IR-tablets should be stored in the original container, and the storage temperature should not exceed 25°C. The tablets should be stored in the original packaging in order to protect them from moisture.

7.10. Blinding and procedures for unblinding

Not applicable – this is an open-label study.

7.11. Concomitant treatments

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

No medications (with the exception of acetaminophen (paracetamol) up to 2 g/day), will be allowed while the subject is participating in the study, except those medically indicated for the treatment of AEs. If any medication is required, the subject may be withdrawn from the study at the discretion of the Investigator and the Sponsor, if use of that medication could compromise the safety of the subject or the scientific value of the trial. No dietary supplements or herbal remedies which are known to interfere with the CYP3A4 metabolic pathway and/or P-gp transport 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 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 dose of study medication will be documented as a prior medication. Medications taken after the 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 16.1.

8.2. Timing of Assessments

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

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

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:

- 12-lead ECGs (single readings, with the exception of triplicate reading at screening and pre-dose)
- HR/BP (single readings, with the exception of triplicate reading at screening and pre-dose)
- AE monitoring (spontaneous and solicited AE monitoring will include specific questioning for tolerability and safety)
- PK blood sampling (at the nominal time)
- Laboratory safety blood and urine samples
- Physical examinations

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 time windows for study assessments are detailed in Section 8.8 of this protocol.

To minimise variability, throughout the study, study staff should ensure a minimum 10-minute supine period before the following assessments: BP, HR, ECG; the rest period is also recommended before drawing blood samples.

Throughout the study from the point of signing the ICF AEs will be documented as they are reported by the subjects. Subjects will also be questioned about AEs at the times that blood samples are taken, at follow-up, and at the specific time points detailed in the Schedule of assessments (Section 5).

8.3. Screening Visit

All subjects will be screened within 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, within the allowed 4 weeks of screening period.

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

The following assessments will be done 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 (i.e., prescription or non-prescription drugs, and dietary supplements taken within 28 days before the planned dose)
- Full physical examination, including body weight and height: see Section 8.11.3
- Vital signs (BP and HR): see Section 8.11.2;
- 12-lead ECG: see Section 8.11.1
- AE monitoring (spontaneous and solicited AE monitoring will include specific questioning for tolerability and safety)
- Urinary drug screen (opiates, amphetamines, barbiturates, cannabis, benzodiazepines and cocaine-metabolites) and breath test for alcohol
- Blood sampling for serology (HIV and hepatitis)
- Blood sampling for clinical safety laboratory evaluations:
    - Haematology: haemoglobin, haematocrit, MCV, MCH, MCHC, platelets, reticulocytes, WBC including differential, RBC;
    - Coagulation: aPTT, PT;
    - Biochemistry: serum AST, ALT, AP, GGT, LDH, CK, amylase, lipase, glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium;
    - Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites. Microscopy will be done only if the dipstick test for protein, blood, leukocyte esterase or nitrites is abnormal.

To prepare for study participation, subjects will be instructed on the unit- and study-specific restrictions described in Section 4.3 (Dietary and lifestyle guidance).

8.4. Admission to Ward (Day –1)

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

Subjects will fast according to the requirements in Section 4.3.

8.5. Profile day (Day 0)

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. Subjects taking Treatment D and E will consume breakfast before their dose (see Section 4.3). Emodepside will be administered, with approximately 240 mL of water[21], between 0800–1100 h. The following assessments will be done before and/or after dosing at the time points given in the Schedule of assessments (Section 5).

- Scheduled AE monitoring
- 12-lead ECGs
- Vital signs (BP and HR)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis)
- Blood sampling to assay emodepside in plasma

8.6. Post-dosing days (Days 1–3)

Subjects will remain on the ward until the morning of Day 3, and have the following assessments at the time points given in the Schedule of assessments (Section 5).

- Scheduled AE monitoring
- 12-lead ECG
- Vital signs (BP and HR)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, urinalysis)
- Blood sampling to assay emodepside in plasma
- Brief (directed) physical examination and short neurological examination

A full neurological examination may be conducted, as required.

8.7. Outpatient (ambulatory) visit (Day 5) and Follow-up visit (Day 7)

Subjects will return to the clinic for an outpatient visit and the Follow-up Visit, as scheduled in the Schedule of assessments (Section 5). The following assessments will be done.

- Scheduled AE monitoring
- 12-lead ECG
- Vital signs (BP and HR)
- Clinical safety laboratory evaluations (haematology, coagulation, biochemistry, and urinalysis)
- Blood sampling to assay emodepside in plasma
- Physical examination (brief or full) and short neurological examination

A full neurological examination may be conducted, if clinically indicated or to investigate treatment-emergent adverse events.

8.8. 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 8.10 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 in the ward, and additional outpatient visits, will be permitted in the event of a technical failure, and/or if extra observations or samples of blood are needed for safety purposes.

In the case of any post-dose samples for PK 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 dosing;
- Deviations of not more than 15 min on measurements scheduled from after 4 h to 24 h after dosing;
- Deviations of not more than 1 h on measurements scheduled more than 24 h after dosing; and
- Deviations of not more than 3 h on measurements scheduled on Day 5 and Day 7.

For all other procedures (including pre-dose PK sample), the following will not be regarded as protocol deviations:

Table 3. Permitted allowed time windows for all other procedures

Time point (Day 0)	Deviation window in relation to the scheduled time point
Pre-dose	Within 75 min before dosing[1] (Part 1b: all procedures to be completed before breakfast)
Up to and including 4 h after dosing	± 10 min
After 4 h to 24 h after dosing	± 15 min
More than 24 h after dosing	± 1 hour
Ambulatory visits	Any time on the scheduled day

1. Urine collection for laboratory safety tests will be within 2 h of the scheduled time point and Day 0 urine sample to be collected pre-dose.

8.9. PK assessments

Blood samples for assay of emodepside will be collected at the time points indicated in the Schedule of assessments (Section 5). The exact date and time of PK blood sampling will be recorded in the CRF.

Blood samples for emodepside assay will be taken from either arm. Samples will be collected either via a cannula 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 Table 4.

Plasma will be analyzed for emodepside using a validated assay method. Full details of the method will be presented in a separate document and all the results will be reported in the bioanalytical report at the end of the study. On the Profile Day (Day 0), frequent blood samples will be collected for PK estimation and emodepside plasma concentrations. The following PK parameters of emodepside will be derived for each subject:

Pharmacokinetic parameters

Text Symbol	Definition	Calculation
Concentrations and times		
C_{max}	Maximum (peak) plasma concentration	The maximum (peak) plasma concentration will be obtained directly from the concentration–time data.
C_{max}/Dose	Dose-normalised C_{max}	The dose-normalised C_{max} will be calculated as C_{max} /Dose administered
$C_{max,norm}$	Observed maximum plasma concentration corrected by dose and body weight	The C_{max} normalised by dose and body weight will be calculated as C_{max}/(Dose administered*body weight)

Text Symbol	Definition	Calculation
t_{max}	Time to reach maximum (peak) plasma concentration	The first time of maximum (peak) plasma concentration will be obtained directly from the concentration–time data.
Half-life		
λ_Z	Terminal rate constant	The apparent terminal phase rate-constant (λ_Z) will be estimated by linear regression of logarithmically transformed concentration versus time data.
$t_{1/2,0\text{-}24h}$	Dominant half-life	The half-life calculated from the terminal slope of the log concentration-time curve (0–24 h), as follows: $t_{½} = \frac{\log_e 2}{\lambda_z}$
$t_{1/2}$	Terminal elimination half-life	The terminal half-life calculated from the terminal slope of the log concentration-time curve, as follows: $t_{½} = \frac{\log_e 2}{\lambda_z}$
Points terminal	Number of points for λ_z	The number of time points used in calculating λ_Z
Areas under the curve		
AUC_{last}	Area under the plasma concentration-time curve from time zero to time of last measurable concentration	The area under the concentration-time curve from zero time (pre-dose) to the time of last quantifiable concentration will be calculated using the (specified) trapezoidal method.
$AUC_{0\text{-}7d}$	Area under the plasma concentration–time curve from time zero to 7 days	The area under the concentration-time curve from zero time (pre-dose) to 7 days will be calculated using the (specified) trapezoidal method. If λ_z is not estimable, a partial AUC is not calculated (when $t_{last}<t$).
$AUC_{0\text{-}7d}$/Dose	Dose-normalised AUC from time zero to 7 days	The dose-normalised AUC from time zero to 7 days will be calculated as $AUC_{0\text{-}7d}$/Dose administered
$AUC_{0\text{-}7d,norm}$	Area under the concentration-time curve from time zero to 7 days corrected by dose and body weight	The AUC from time zero to 7 days normalised by dose and body weight will be calculated as $AUC_{0\text{-}7d}$/(Dose administered*body weight)
Mean residence time		
MRT_{last}	Mean Residence Time	The mean residence time will be

Text Symbol	Definition	Calculation
		calculated using: $MRT = \frac{AUMC}{AUC_{last}}$

8.10. 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 planned total blood volume to be taken from each subject during the study is 158 mL.

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

Table 4. Blood volumes

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Haematology	7	2	14
Biochemistry	7	2.5	17.5
Coagulation	7	3	21
Serology	1	2.5	2.5
Emodepside PK	18	5	90
Discard (when using a cannula)	13	1	13
		Total	**158 mL**

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

8.11. Assessment of Safety

Safety of the treatments will be assessed through routine monitoring of adverse events.

From screening (for AE onset after the subject signs the ICF), daily during the in-patient phase, then at the outpatient and Follow-Up Visits, the patients will be enquired about current adverse events or any events observed during the period previous to the visit.

In addition, 12-lead ECG recording, regular measurement of vital signs and physical examinations, clinical laboratory parameters monitoring, will be made at scheduled follow-up visits. (See Section 9 for AE recording and reporting, and the descriptions

below.)

8.11.1. 12-lead ECG Safety recording

Standard 12-lead ECGs will be recorded at the times given in the Schedule of assessments (Section 5). Triplicate ECGs will be done at screening (about 1 minute between recordings); single readings will be done at all other time points. 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 adverse event (see AE definition in Section 9.1). If out of range at screening, the ECG may be repeated once.

8.11.2. Vital signs

BP and HR will be measured, in the supine position after 10 minutes rest, at times detailed in the Schedule of assessments (Section 5).

BP and HR will be measured using using SpaceLabs oscillometric equipment.

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

- Supine systolic BP: 85 – 160 mm Hg
- Supine diastolic BP: 40 – 90 mm Hg
- Supine HR: 35 – 100 beats/min

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 adverse event) and decide on an appropriate course of action. If out of range at screening, vital signs may be repeated once.

Oral temperature will be measured using oral thermometers.

8.11.3. Physical examination and neurological 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.

At certain time points, as detailed in the Schedule of assessments (Section 5), a brief (symptom-directed) physical and short neurological examination will be performed.

Height and body weight will also be measured at screening; body weight will be measured on Day –1.

Neurological examination will be done by a physician, in case it is clinically indicated, or to investigate treatment-emergent AEs. At the time-points in the Schedule of assessments (Section 5), a short neurological examination will be done, which includes an informal psychological assessment (e.g. orientation to place and time). Any abnormalities will trigger the full neurological examination or opening of an AE as appropriate. The full neurological examination may include (but is not limited to) any of 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. Abnormalities assessed as clinically significant will be reported as adverse event (see AE definition in Section 9.1).

8.11.4. 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 Reference 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). Data from analysers that are not interfaced will be entered manually into the LIMS. Confirmed abnormal laboratory results (after repeat) will be assessed for clinical significance and reported as AEs if necessary.

Collection of samples for laboratory safety tests: Blood will be taken for haematology (2 mL in EDTA), and biochemistry (2.5 mL in tubes with a gelatin plug), and coagulation (3 mL in sodium citrate). At screening, blood will be taken for serology (2.5 mL in tubes with a gelatin plug). 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 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 lab, a clinical diagnosis should be recorded rather than the abnormal value itself, if available (for example, "anaemia" rather than "decreased red blood cell count").

9. Adverse Event definitions and reporting

9.1 Adverse Event definition

An *adverse event* will be defined as:

Any untoward medical occurrence in a clinical trial subject administered a medicinal product that does not necessarily have a causal relationship with that treatment. An AE can therefore be any unfavourable and unintended sign (e.g. 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 (i.e., ECG, X-ray, etc.) or laboratory results which are assessed as "clinically significant". Information on AEs must be evaluated by a physician. Each AE is to be classified by the

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

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.

9.2 Serious Adverse Event (SAE)

An AE will be defined as serious if it:

- **results in death**

  i.e. 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**

  i.e. 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 (i.e. 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**

  i.e. 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 adverse event/reaction.

9.3 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 assessments (Section 5).

Each AE will be assessed for severity, and causality (see definitions in Section 9.6 and 9.7). In addition, each AE is to be classified by the Investigator as serious or

non-serious (see definition in Section 9.2). This classification will determine the reporting procedure for the event (see Section 9.5).

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 adverse events are to be reported on the CRF, which is to be submitted to DNDi as specified in Section 13.2. 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.

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

9.4 Adverse Event reporting period

The adverse events reporting period begins upon subject enrolment in the trial (after signature of the ICF) and ends at the Follow-up Visit.

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

In addition, any AE that occurs subsequent to the AE reporting period that the Investigator assesses as possibly related to the investigational medicinal product should also be reported as an AE.

9.5 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 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 REC of SAEs 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 IMP (as defined in Section 9.7) 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 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 calendar days** after DNDi becomes aware of the event.

9.6 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 CRFs. 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 (e.g. 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.

9.7 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, i.e. 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 IMP. 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.

9.8 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 90 days after the 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 90 days after administration of the 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 (i.e. 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.

9.9 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 (i.e. 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 IMP 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).

10. 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.

It may be appropriate for the subject to return to the clinic for final safety assessments which may include all assessments normally scheduled for the study Follow-up visit (See the Schedule of assessments [Section 5]).

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 and PK data, which should be collected if possible and in accordance with additional 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-emergent AE (TEAE), thorough efforts should be made to clearly document the outcome of that TEAE.The Investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved TEAEs.

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

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

- 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.

11. 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.

11.1. Sample size determination

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

10 subjects per treatment arm is considered sufficient to examine the safety and tolerability of emodepside, as well as the PK after single doses. However, 12 subjects will be recruited and enrolled per treatment arm to ensure a minimum of 10 evaluable subjects complete the study.

11.2. 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 PK sample has been analysed.
- PK Parameter Population: All subjects in the PK Concentration Population for whom PK 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 (e.g. 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.

11.3. Subject Disposition

The disposition of all subjects in the safety population will be summarized including: number of subjects randomized (or treated, for non-randomised groups); 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.

11.4. Efficacy Analysis

Not applicable.

11.5. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (e.g. medical history, physical examination, vital signs, weight and ECGs) 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.

11.6. 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;
- AEs.

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

11.6.1. 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 1 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[22,23]. 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.

Abnormal physical examination findings (with or without clinical significance) will be listed.

11.6.2. Haematology, Coagulation 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 (i.e. haematology or clinical chemistry). Frequencies of laboratory values of potential clinical importance will be summarised.

11.6.3. Urinalysis parameters

These parameters will be individually listed and summarized.

11.6.4. Physical and neurological examination

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

11.6.5. 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 13.2.

Adverse events 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 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 on the dosing day, the AE will be considered as a 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 serious adverse events will be listed separately (fatal events will be listed separately from non-fatal events).

11.7. 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[23]; 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 will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically.

To assess the relative bioavailability, analysis of variance (ANOVA) models will be fitted to the tablet (test) and solution (reference) data with the logarithm of the pharmacokinetic parameters $AUC_{0\text{-}7d}$/Dose or C_{max}/Dose as the dependent variable, and formulation as a fixed effect. The point estimates least squares (LS)-means and 90% confidence intervals for the ratios “B / A” and “C / A” will be calculated in Part 1a. In Part 2, “F/A” and/or “G/A” will be calculated. The acceptance range 80 – 125% will be applied for these assessments.

To assess the effect of food, ANOVA models will be fitted to the data with the logarithm of the pharmacokinetic parameters $AUC_{0\text{-}7d}$/Dose or C_{max}/Dose as the dependent variable, and fed (test) or fasted (reference) as a fixed effect. In Part 1, the point estimates and 90% confidence intervals for the ratios “D/B” and “E/C” will

be calculated. The acceptance range 80 – 125% will be applied for the assessment of a potential food effect.

To assess dose proportionality, for each tablet type, exploratory ANOVA models will be fitted to the relevant fasted data in Parts 1 and 2 with the logarithm of the pharmacokinetic parameters $AUC_{0\text{-}7d}$ or C_{max} as the dependent variable and dose as a fixed effect. The ratios “F/B” and/or “G/C” will be calculated.

12. Safety Review Meetings

Safety will be reviewed between Part 1 and Part 2 of the study in a Safety Review Meeting. Participants in the Safety Review Meeting (‘the Safety Review Group’ [SRG]) 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. This meeting will follow DNDi SOP CL 26 (Safety Data Review during Phase I clinical trial) and will be described in the Safety Review Group charter.

13. Quality Assurance and Quality Control Procedures

13.1. 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.

13.2. Case report forms

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 CRF or the screening section of the study-specific CRF and additional source documents. The CRF is the source document for the majority of recorded data. Source documents other than the CRF will be predefined in the Source Data Agreement.

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

The Investigator 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 screened subjects who leave

the study before enrolment, will be recorded in the CRF but not entered in to the database.

13.3. Source documents

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

The Investigator must maintain source documents 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.

13.4. 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.

13.5. Monitoring, audits and inspections

Monitoring visits to the trial site will be made periodically by DNDi representatives or designated clinical monitors to ensure that GCPs 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/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 CRFs 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.

13.6. 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 REC.

The Investigators will permit representatives of DNDi and/or designated clinical monitors to inspect all CRFs and 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.

13.7. 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.

13.8. 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/other forms 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.

14. 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 (e.g. 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.

15. 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 Drug Safety and Monitoring Board 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 Visit are followed up with the necessary medical care.
- Provide in writing the reasons for the decision to the national health authority and the Sponsor.

16. 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)[24]. 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 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 REC and subsequently by the 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 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 ICF which has been approved by London – Brent REC 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 9.5), 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 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 serious adverse event that occurs during this trial (see Section 9.5). The Investigator will provide the REC with annual progress reports of the trial, if the trial lasts longer than a year.

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 of the clinical trial report 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.

16.1. 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.

16.2. Compensation of volunteers

The Sponsor agrees to abide by the Association of the British Pharmaceutical Industry Guidelines for medical experiments in healthy human volunteers (2012 edition)[24] 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.

16.3. 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.

16.4. 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 IMP, DNDi should be informed immediately.

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

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

16.5. 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.

17. References

1. WHO. Global programme to eliminate lymphatic filariasis: progress report 2014. Wkly. Epidemiol. Rec. 90, 489–504 (2015).
2. Zouré, H. G. M. et al. The Geographic Distribution of Loa loa in Africa: Results of Large-Scale Implementation of the Rapid Assessment Procedure for Loiasis (RAPLOA). PLoS Negl. Trop. Dis. 5, e1210 (2011).
3. Vos, T. et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 386, 743–800 (2015).
4. Organisation Mondial de la Santé (OMS). Progress report on the elimination of human onchocerciasis, 2015-2016. 91, 501–516 (2016).
5. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. ICH Guidance for Industry E14, 2005.
6. Okoye, I. C. & Onwuliri, C. O. Epidemiology and psycho-social aspects of onchocercal skin diseases in northeastern Nigeria. Filaria J. 6, 15 (2007).
7. Amazigo, U. O. Detrimental effects of onchocerciasis on marriage age and breast-feeding. Trop. Geogr. Med. 46, 322–325 (1994).
8. Alonso, L. M., Murdoch, M. E. & Jofre-Bonet, M. Psycho-social and economic evaluation of onchocerciasis : a literature review . Soc. Med. 4, 8–31 (2009).
9. WHO. Working to overcome the global impact of neglected diseases - summary - First WHO report on neglected tropical diseases. (2010).
10. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England) 388, 1603–1658 (2016).
11. Plaisier, A. P., van Oortmarssen, G. J., Remme, J. & Habbema, J. D. F. The reproductive lifespan of Onchocerca volvulus in West African savanna. Acta Trop. 48, 271–84 (1991).
12. Schulz-Key, H. & Soboslay, P. T. Reproductive Biology and Population Dynamics of Onchocerca Volvulus in the Vertebrate Host. PARASITE Biol. Biochem. 1, 53–55 (1994).
13. Hotez, P. J. & Kamath, A. Neglected tropical diseases in sub-saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis 3, e412 (2009).
14. Meredith, S. E. & Dull, H. B. Onchocerciasis: The First Decade of MectizanTM Treatment. Parasitol. Today 14, 472–474 (1998).
15. Fobi, G. et al. Managing the Fight against Onchocerciasis in Africa: APOC Experience. PLoS Negl. Trop. Dis. 9, e0003542 (2015).
16. Gardon, J. et al. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. Lancet 350, 18–22 (1997).
17. Zahner et al. Filaricidal efficacy of anthelmintically active cyclodepsipeptides. Int J Parasitol. 31, 1515-22 (2001).
18. Zahner et al. Effects of Bay 44-4400, a new cyclodepsipeptide, on developing stages of filariae (Acanthocheilonema viteae, Brugia malayi, Litomosoides sigmodontis) in the rodent Mastomys coucha. Acta Tropica 80,19-28 (2001).
19. Willson, et al. The effect of the anthelmintic emodepside at the neuromuscular junction of the parasitic nematode Ascaris suum. Parasitology 126, 79-86

(2003).
20. Guest, et al. The calcium-activated potassium channel, SLO-1, is required for the action of the novel cyclo-octadepsipeptide anthelmintic, emodepside, in Caenorhabditis elegans. Int J Parasitol. 37, 1577-88 (2007).
21. Committee for Human Medicinal Products (CHMP) Guideline on the investigation of drug interactions. CPMP/EWP/560/95/Rev. 1 Corr. 2. European Union 2012.
22. Statistical principles for clinical trials. ICH harmonised tripartite guideline E9, 1998.
23. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. ICH Guidance for Industry E14, 2005.
24. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)
25. Guidelines for Phase 1 Clinical Trials, 2012 Edition. Association of the British Pharmaceutical Industry.