DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL SYNOPSIS

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

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
Protocol Number	DNDI-EMO-02
Sponsor	DND*i*, Chemin Louis Dunant, 15, 1202 GENEVA Switzerland Phone : +41 22 906 9230
Principal Investigator	[redacted]
SAC approval	22 June 2017
Clinical Trial Protocol Synopsis Version / Date	Version 1.0, 17 July 2017

SYNOPSIS

Background Information and Trial Rationale	**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% 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). Severe visual impairment and blindness are considered the most severe complication 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. The burden associated to onchocerciasis is estimated at more than 1 million disability-adjusted life years (DALYs) in 2013 worldwide[7]. *Onchocerca 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 in the host, the larvae molt twice before reaching the adult stage. The average reproductive life span of an adult female worm in the human body is estimated to 10 years[8] 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[9] new microfilariae (first stage larvae, L1) per day (however, in *O. volvulus*, the release of microfilariae by the female worms is not constant and one estimates that there are in 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 molting 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 of onchocerciasis patients. The drug kills the microfilarial stage of the parasite and provides temporary sterilization of adult female worm, preventing vector-borne transmission and re-population of the host's skin with microfilariae for several months only. 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 preventive 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[10] to African Control programs in 24 African countries under the direction of APOC/ WHO until 2015[11]. 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 production of new microfilaria 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 is another filarial disease also called "eye worm" and occurs exclusively in West and Central Africa; an estimated 13 million people are infected with *Loa loa*[15]. 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[12]. 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[13]. *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[14,15]. 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 *Onchocerca volvulus* as explained below. The study described in the present synopsis investigate the safety, tolerability and pharmacokinetics of emodepside (BAY44-4400) after multiple doses, in healthy male Caucasian subjects.
Rationale for the Development of Emodepside	**Emodepside** Emodepside (BAY 44-4400) Emodepside is a registered drug for animal health, commercialized by Bayer Animal Health GmbH under the name of Profender® (in combination

	with praziquantel) or Procox® (in combination with toltrazuril). Emodepside was shown to be macrofilaricide 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*[16, 17]. 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[18]. 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)[19]. 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 as 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 and is currently under evaluation. As the study is still ongoing, treatment allocation has not yet been fully unblinded; however, the first 8 dose steps from 1 to 40 mg single dose have been unblinded and evaluated with respect to safety, tolerability and pharmacokinetics; the results are favourable support continuing the phase I development program and merit the further development of emodepside. Details of those interim results are presented in the Summary of Clinical Human Data section below. In the present repeat dose study, pharmacokinetic as well as safety and tolerability of the liquid service formulation of emodepside, given over 10 days will be tested.
Summary of Non-Clinical Information	<u>Summary of Pharmacology Data</u> 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 MIC_{100} value for motility was 0.1 µM emodepside that is 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 i.e., *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 *Onchocerca 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 anthelminthic activity. Furthermore, emodepside statistically 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., microfilaria and adult filarial nematodes *in vitro* and thus, non-clinical pharmacology data of emodepside supports its use for treatment of onchocerciasis in humans. A large number of safety pharmacology studies were performed *in vitro* (+ mechanistic studies) and *in vivo* in rats and dogs. In addition, standard safety pharmacology parameters were included in the toxicity studies with emodepside in rats and dogs. The in vitro hERG assay showed no critical potential for QT prolongation (IC20 19 µM). *In vitro*, emodepside weakly inhibited GABA-A receptor (46% at 10 mmol/L). In pituitary neuroendocrine preparations, 500 nmol/L emodepside reduced GABAergic activity. Safety pharmacology and repeated dose toxicity studies revealed the central nervous system as a target organ with changes in behaviour, activity, tremor and gait abnormalities in rats, mice and dogs. A No Observed Adverse Effect Level (NOAEL) of 5 mg/kg i.d. was defined in dogs and rats after repeated administration (4-week repeat oral dose toxicity study). 10 mg/kg body weight was established as NOEL for effects on the nervous system in fasted rats after acute administration. TK analysis suggested an AUC of 1,611 ng.h/mL and Cmax 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 Cmax 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 bodyweight [bw]). Also in dogs, no effect on respiratory functions was observed at the tested doses. Hyperglycaemia was observed in rats in acute and repeated dose 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 the ECG in anesthetized dogs. However, a moderate vasodilatation (reduction of total resistance, slight decrease of arterial blood pressure, moderate, probably reflex tachycardia) was observed at ≥1.5 mg/kg body weight. A threshold plasma level of 0.1 µg/mL was determined for this effect. The clinical significance of the vasodilatory effects is unclear as no effect on blood pressure or heart rate was seen in dogs following oral administration of emodepside for 4 weeks

at up to 20 mg/kg body weight.

Summary of Pre-Clinical Pharmacokinetic Data

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

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

Biodistribution studies with ^{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 fecal/biliary route (about 50% within 24 h, 83–93% within 168 h), with only 2-3% of the dose being found in urine. The unchanged compound emodepside accounted with 45-56% for most of the dose excreted into feces. 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.

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

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 bw, 800 ppm equals in rats approx. 77-95 mg/kg bw, both in 13-week treatment schedule). The studies in rats revealed toxicities resulting from metabolic changes induced by emodepside indirectly, such as a decrement in bodyweight gain but in parallel an increased feed and water consumption as well as deformation of teeth as a sign of a diabetic-like effect. The main affected organs were kidney, pancreas and liver, with associated changes in haematological parameters, triglyceride and glucose levels in the plasma and lipid and glycogen stores. These toxicological findings pointed to a diabetes-related condition (inhibition insulin secretion followed by increased glucose levels, reduced leptin levels, as confirmed by mechanistic studies). In mice, the NOAEL after 14 week of treatment was 50 ppm (10.5-16.8 mg/kg bw.). The NOAEL in the 14-week rat study was defined at 10 ppm (m: 0.73, f: 1.11 mg/kg bw per day); In 4-week rat studies 50 ppm (equals 4 – 5 mg/kg bw) was defined as NOAEL. In dogs, doses starting from 10 mg/kg bw per day for 4 weeks resulted in clinical signs like vomiting, tremor and unsteady gait. At 20 mg/kg bw, an effect on nutritional state, food intake and bodyweight gain was noted. All effects were reversible after a recovery period of 4 weeks. The NOAEL for this study was 5 mg/kg bw. Several reproductive and developmental toxicity studies were conducted in rats and rabbits. Effects of emodepside on the reproductive performance in rats occurred only at parentally toxic doses. No primary effect on fertility and reproduction was observed. In this species, both ovarian weight and gestation rate were unaffected by treatment. Primary systemic parental effects were due to diabetes I like effects, which were well known from repeat dose studies in rats. A battery of well-conducted, GLP-compliant teratogenicity studies revealed maternal toxicity, fetotoxicity, foetal malformations and various skeletal/visceral anomalies or deviations. Clinical signs of systemic maternal toxicity were evident at dose rates ≥6 mg/kg bw. Overall, severe maternal toxicity at 18 mg/kg bw resulted in adverse effects on foetal development. The NOAEL for maternal toxicity in rats was 2 mg/kg bw and the NOAEL for developmental toxicity was 0.5 mg/kg bw. However, as discussed above, diabetes like effects, which were not measured in developmental toxicity studies, occurred in lower dosages. Therefore, it can be assumed that the maternal toxic dose was significantly lower (NOEL of 1 mg/kg bodyweight in safety pharmacology studies on glucose levels in the blood. See also glucose level in pregnant rats). In rabbits, the effects were similar to the rat studies. The NOEL for developmental toxicity in the rabbit was 5 mg/kg bw. Additional endocrinology studies confirmed the involvement of emodepside in hormone deregulation (reduced estradiol [E2], triiodothyronine [T3], insulin, leptin and prolactin levels and enhanced thyroid-stimulating hormone [TSH] and glucagon levels) while not having estrogenic/anti-estrogenic or androgenic/ anti-androgenic potency. This deregulation is assumed to be the cause for the observed developmental toxicity. In vitro and in vivo genotoxicity studies revealed no mutagenic potential for emodepside; no carcinogenicity studies were conducted. Local tolerance

	studies in rats and rabbits revealed no skin- or eye-irritating potential of emodepside. In guinea pigs, emodepside was found to have no skin sensitization potential. General Pre-Clinical Summary The non-clinical data package of emodepside is comprehensive due to the authorization of 3 veterinary medicinal products (Profender Spot-on, Profender Tablets, Procox). The safety pharmacology studies, ADME studies, acute and repeated-dose studies, studies on reproduction and development, genotoxicity studies, local tolerance and sensitization studies as well as mechanistic studies on the toxicological mode of action are included in the submission package. All these non-clinical studies (all pivotal studies were conducted under GLP conditions) are sufficiently supporting this phase I study in human subjects.

Summary of Clinical Human 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 emodepside Liquid Service Formulation (LSF) solution or immediate release (IR) tablets (dose range 1.0 mg–40 mg LSF solution, and doses of 5 mg and 20 mg tablets) or placebo, in fasted condition; or for the 8 subjects of cohort 9 to 10 mg LSF solution or placebo after a high-fat, high calories breakfast.

Based on the data available so far, 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 (cohorts 1-8, 63 subjects randomized) 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).

Total number of subjects with at least one TEAEs – by SOC

SOC	*Placebo*		*Emodepside*									*Total N=63 n (%)*
	LSF N=12 n (%)	tablet n=4 n (%)	0.1 mg LSF N=1 n %	1 mg LSF N=5 n (%)	2.5 mg LSF N=6 n (%)	5 mg LSF N=6 n (%)	5 mg tablet N=5 n (%)	10 mg LSF N=6 n (%)	20 mg LSF N=6 n (%)	20 mg tablet N=6 n (%)	40 mg LSF N=6 n (%)	
Any TEAE	**5 (41.7)**	**1 (25.0)**	**1 (100.0)**	**3 (60.0)**	**0**	**3 (50.0)**	**3 (60.0)**	**5 (83.3)**	**3 (50.0)**	**2 (33.3)**	**5 (83.3)**	**31** (49.2)
Eye disorders	0	1 (25.0)	0	0	0	0	1 (20.0)	2 (33.3)	1 (16.7)	0	5 (83.3)	**10** (15.9)
Gastrointestinal disorders	1 (8.3)	1 (25.0)	0	0	0	1 (16.7)	0	0	0	1 (16.7)	0	**4** (6.3)
General disorders and administration site conditions	0	0	0	0	0	2 (33.3)	0	0	0	0	0	**2** (3.2)
Infections and infestations	0	0	1 (100.0)	0	0	1 (16.7)	0	1 (16.7)	1 (16.7)	0	1 (16.7)	**5** (7.9)
Injury, poisoning and procedural complications	1 (8.3)	0	0	0	0	0	0	0	1 (16.7)	0	0	**2** (3.2)
Musculoskeletal and connective tissue disorders	0	0	0	1 (20.0)	0	1 (16.7)	1 (20.0)	0	0	1 (16.7)	1 (16.7)	**5** (7.9)
Nervous system disorders	2 (16.7)	0	0	2 (40.0)	0	1 (16.7)	1 (20.0)	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)	**12** (19.0)
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)

Across all treatments within Part 1 (Cohorts 1-8), no serious adverse events were reported. Overall, 51 non-serious adverse events (AEs) were reported by 31 out of the 63 subjects (49%), of which 43 non-serious AEs reported by 25 out of the 47 subjects (53%) exposed to emodepside and 8 non-serious AEs reported by 6 out of the 16 subjects (37%) exposed to placebo. All TEAEs (related or not) were mild or moderate in severity.

A total of 14 subjects (22.2%) experienced 20 TEAEs that were considered by the investigator to be related to emodepside treatment.

Non-serious eye disorders AEs were reported in 9 out of 47 subjects receiving emodepside, and included: vision blurred (n=5 subjects), photophobia (n=2), visual impairment (n=2), accommodation disorder (n=1), whereas 1 out of 16 subjects receiving placebo reported dry eye (n=1). All eye disorders AEs were of mild to moderate intensity, resolved spontaneously (without treatment), and were more frequently reported with highest dose (40 mg). Among them, the AEs of blurred vision, photophobia ("Increased ocular light sensitivity"), visual impairment ("distorted contrast perception", "distorted color 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), lightheadness (n=1), dizziness (n=1) or headache (n=1) were reported concomitantly to blurred vision.

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

The pharmacokinetic results obtained so far show that T_{max} for the LSF solution is consistently about 1 h post-dose when fasted. Mean C_{max} and AUC for the LSF solution have been roughly dose-proportional, with low to moderate inter-individual variability. The plasma half-life during the first 24 hours is very short for a single dose of emodepside. After 3, 7, 16 and 47 hours the maximum plasma concentration is reduced to 50%, 25%, 12.5% and 6.25% respectively. Terminal plasma half-life is 523 hours. Although data of cohort 9 (which was treated with a single dose of emodepside with food) are still blinded, 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%, Cmax to 42% and a delay of the Tmax up to 2.33 hours. 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 insulinemia below 13 pmol/L was reported, with a maximum between 0 and 4 hours. 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 hours (none of these events were considered as clinically significant by the investigator and therefore they were not reported as AE) and a maximum of 12.7 mmol/L at 2 hours at the dose of 40 mg LSF solution. In fasted conditions, both blood insulin decrease and glucose increases occurred over the 4 hours after single dosing with emodepside in most cases. There was no report of other clinically significant abnormalities in any laboratory parameters.

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

	Data of cohort 10 (treated with a single 40 mg dose of emodepside and focused at ocular system assessment) are still blinded, however no serious adverse events were reported following administration of the LSF of 40 mg. Overall, 28 non-serious adverse events (AEs) were reported, all mild or moderate in severity. Five subjects reported blurred vision or visual perception disorders, e.g. increased colour vividness or altered perception of dimensions, with an onset in most case close to Tmax and of various durations. In addition, 2 subjects reported concomitant sense of relaxation, 1 subject reported dizziness, 1 subject reported disturbance in attention and hypervigilance and 1 subject reported concomitant sense of imbalance. Also 1 subject reported tongue paresthesia that lasted for approximately 6 hours.
Trial Objectives	**Primary Objective:** • To investigate the safety and tolerability of emodepside (BAY44-4400) after multiple doses, administered as a LSF oral solution, in healthy male Caucasian subjects **Secondary Objectives:** • To investigate the PK of emodepside (BAY44-4400) after multiple doses, administered as an LSF oral solution. • To investigate the time-matched profiles of selected PD markers in plasma after multiple doses of emodepside (BAY44-4400), administered as an LSF oral solution.
Trial Endpoints	**Safety and Tolerability Variables:** • Adverse events (AEs) • Physical and neurological examination findings (including assessments of tremor of the hands and fingers, coordination/cerebellar function (finger to finger, finger to nose, with eyes open and closed), pupil size and reaction to light) • Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP) • 12-lead ECG (including HR, PR, QRS, QTcB, QTcF) • Clinical laboratory tests: Haematology: haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets, reticulocytes, white blood cells (WBC) including differential, red blood cells (RBC), glycated haemoglobin (HbA1C) (at screening); Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT); Biochemistry: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), amylase, lipase, free T3 and T4, thyroid-stimulating hormone (TSH), glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride, and magnesium; At baseline and day 9 additional hormones: leptin and prolactin levels Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites. • Ophthalmology assessments, including visual symptoms, past ocular

	history, best corrected distance visual acuity, colour vision assessment, Amsler grid assessment **Pharmacodynamic Variables:** • Time-matched profiles of glucose, glucagon, insulin, and cortisol. • Oral glucose tolerance test (OGTT) **Pharmacokinetic Variables:** Emodepside plasma concentration–time data will be used to derive the following PK parameters of emodepside: • After a single dose of emodepside (Day 0): o Main PK parameters: AUC_{tau}, AUC_{tau}/D, C_{max}, C_{max}/D o Exploratory PK parameters: $AUC_{tau,norm}$, $C_{max,norm}$, T_{max}, MRT_{tau}, Vz/f • After multiple doses of emodepside (Day 9): o Main PK parameters: AUC_{∞}, AUC_{∞}/D, AUC_{tau}, AUC_{tau}/D, $C_{max,ss}$, $C_{max,ss}/D$ o Exploratory PK parameters: $AUC_{\infty,norm}$, $AUC_{tau,norm}$, AUC_t, AUC_t/D, $AUC_{t,norm}$, $C_{max,ss,norm}$, $t_{1/2}$, T_{max}, MRT, Vz_{ss}/f, CL_{ss}/f o Other optional parameters: AUC_{t-inf}, %AUCextra, points terminal • Accumulation ratios RA(C_{max}) and RA(AUC_{tau}) will be calculated • C_{trough} will be derived from the concentration data (Days 1–9). The above parameters may be calculated for the metabolites of emodepside, as appropriate. In urine, the amount and concentration of emodepside and possibly its metabolites may be measured. The appropriate specific PK parameters to be calculated will be decided, according to the concentration.
Trial Design	This will be a single-centre, single-blind, randomized, placebo-controlled, parallel-group, multiple-dose, dose-escalation study. The study will evaluate safety, tolerability, PK and PD of emodepside, after administration as an LSF oral solution, over 10 days, in healthy male Caucasian subjects. Treatment duration was defined based on single ascending dose PK data modelling as well as anticipated duration of treatment with emodepside for efficacy. The study will be performed in a single site specialized in Phase 1 studies. Each group will comprise 8 healthy Caucasian male subjects, 6 of whom will be allocated to receive emodepside, and 2 of whom will be allocated to receive placebo. 3 groups will be recruited, to test 3 multiple dose levels of emodepside LSF oral solution. This will be a single-blind study. Where possible, the investigator and sponsor will remain blinded, so as not to potentially introduce bias. Each subject will attend a screening visit within the 4 weeks before their first dose of study medication (on Day 0). Eligible subjects will be admitted to the ward on the evening of Day –3. They will remain on the ward until the morning of day 14 (17 nights in a row), during which they'll receive once- or twice-daily oral doses of emodepside or placebo for 10 days. Safety, tolerability, PD and PK assessments will be done regularly before, during, and after dosing. Each subject will undergo a full day of assessments (excluding PK) on the day before dosing (Day –1), and a similar full day of assessments (including PK) on the first (Day 0) and last days of dosing (Day 9). In

	addition, they will undergo an Oral Glucose Tolerance Test (OGTT) on Day -2, Day 1 and Day 8. Subjects will be discharged from the ward 5 days after their last dose of study medication, if the investigator has no safety concerns. Subjects will attend the ward for out-patient visits on Days 17, 20, 23 and 27(+/- 2 days). Subjects will attend a final follow-up visit on Day 30 (+/- 2 days). 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.
Main Entry Criteria	**Inclusion:** • Male, Caucasian volunteers, deemed healthy based on a clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine. Optionally, after further evaluation during the study, at the sponsor's discretion, other ethnic groups may be recruited. • 18 to 55 years of age. • Normal body weight (BMI; Quetelet index) in the range 18 to 30.1 kg/m^2 at screening. • Sufficient intelligence to understand the nature of the trial and any hazards of participating in it. Ability to communicate satisfactorily with the investigator and to participate in, and comply with the requirements of, the entire trial. • Willingness to give written consent to participate, after reading the information and consent form, and after having the opportunity to discuss the trial with the investigator or his delegate. • Willingness to give written consent to have data entered into the Overvolunteering Prevention System **Exclusion:** • Receipt of a licensed or unlicensed medicinal product as part of another clinical trial within the 3 months prior to, or within 5 half-lives of, their first dose of study medication, whichever is longer, or is currently in the follow-up period for any clinical trial. • Clinically relevant abnormal medical history, concurrent medical condition, acute or chronic illness or history of chronic illness sufficient to invalidate the subject's participation in the trial or make it unnecessarily hazardous. • Surgery (eg stomach bypass) or medical condition that might affect absorption of study drug taken orally. • Presence of abnormal physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the subject. • Blood pressure and heart rate in the supine position at the screening examination outside one (or more) of the ranges 90–140 mm Hg systolic, 60–90 mm Hg diastolic; heart rate 40-100 beats/min. Subjects with vital signs outside the reference range for the population being studied may be included, at the investigator's discretion, if it is unlikely to introduce additional risk and will not interfere with study procedures.

	• Loss of more than 400 mL of blood within 3 months before admission. • Clinically relevant history of vital organ disease or other disease of an organ or the central nervous system. • Medical or psychiatric disorder, condition or history of such (eg seizures) that, in the opinion of the investigator or the sponsor, would increase the risk associated with study participation, or impair the subject's ability to participate or complete this study. • Positive test for hepatitis B, hepatitis C or HIV • Febrile illness within 1 week before the first dose of study medication. • History of severe allergy, non-allergic drug reactions, severe adverse reaction to any drug, or multiple drug allergies. • Subjects with hypersensitivity to any ingredient of the study medication, including the active ingredient, emodepside. • Presence or history of drug or alcohol abuse in the last 10 years, or intake of more than 21 units of alcohol weekly. • Regular daily consumption of more than one liter of xanthine-containing beverages. • Regular daily consumption of more than 5 cigarettes daily, or use more than 3 grams (1/8 ounce) of tobacco. • Use of a prescription medicine during the 28 days before the first dose of study medication or use of an over-the-counter medicine (with exception of acetaminophen (paracetamol)), during the 7 days before the first dose of study medication. • Use of dietary supplements or herbal remedies (such as St John's Wort) known to affect metabolism by CYP3A4 and/or transport by P-gp, during the 28 days before the first dose of study medication (see list in Study Procedures Manual). • Relevant pathological abnormalities in the ECG such as a second or third-degree AV block, prolongation of the QRS complex over 120 msec or QTc-interval over 450 msec (QTcB or QTcF). • Positive test upon drug screening. • Use of excluded therapies that may impact on the interpretation of study results in the opinion of the investigator or sponsor. • Objection by General Practitioner (GP) to subject entering trial. • History of residing for 6 or more continuous months, within the last 3 years, in regions with endemic parasitic infections as determined by the investigator. • Possibility that subject will not cooperate with the requirements of the protocol. • No contact lenses wear within 1 month prior to dosing. Contact lenses wear is not permitted during the study. • Any ocular disorder for which topical ocular therapy is currently or chronically prescribed, including inflammatory eye disease (dry eye allergic conjunctivitis [seasonal allergic conjunctivitis, vernal keratoconjunctivitis,

<table>
<tr><td></td><td>atopic keratoconjunctivitis], uveitis and glaucoma)
• Past history of ocular disease requiring ongoing treatment
• Past ocular surgery including laser or other refractive corneal surgery
• Evidence of eye irritation, visual difficulties, corneal opacity, ocular surface (corneal or conjunctival damage, with or without ocular symptoms)
• Evidence of narrow anterior chamber angles causing increased risk of acute glaucoma
• Evidence of ocular media opacity including lens opacity/vitreous opacities
• Evidence of retinal or optic nerve pathology
• Evidence of pronounced colour blindness, as indicated by an Ishihara score of 9/13 or below</td></tr>
<tr><td>Removal of subjects from study</td><td>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.</td></tr>
<tr><td>Study Duration</td><td>Each subject’s participation in the study will last for up to 9 weeks, and will include a screening visit (within 4 weeks prior to dosing), an in-house 2-week evaluation period (Day –3 to Day 14), followed by 4 outpatient visits (on Days 17, 20, 23 and 27), and a final follow-up visit (on Day 30).</td></tr>
<tr><td>Study treatments</td><td>Test-Drug: Emodepside LSF oral solution (1mg/ml) or matching placebo.
Planned dose levels:
<table>
<tr><th>Group</th><th>Dose level</th><th>Formulation</th></tr>
<tr><td>1</td><td>5 mg, OD, for 10 days</td><td>LSF oral solution (1mg/ml)</td></tr>
<tr><td>2</td><td>10 mg, OD, for 10 days</td><td>LSF oral solution (1mg/ml)</td></tr>
<tr><td>3</td><td>10 mg, BID, for 10 days (single dose on Day 9)</td><td>LSF oral solution (1mg/ml)</td></tr>
</table>
Emodepside administration will be given as fasted doses of LSF oral solution. Each morning dose will be given after an overnight fast of least 8 h. On Days -2, 0, 1, 8 and 9, subjects will fast until at least 4h after dosing. On Days 2 to 7, subjects will fast until at least 1h after dosing. In Cohort 3, subjects will also fast for 2 h before until 2 h after their evening dose.
The dose will not be escalated until the sponsor and investigator have reviewed safety, tolerability and PK data until 48 h after the final dose of study medication in at least 4 subjects on active treatment (ie, at least 6 subjects overall).
The dose will be escalated only if the investigator and sponsor’s medical representative agree that it is appropriate to give a higher dose. The next planned dose level may be reduced, or a dose level may re-tested or an intermediate dose level selected, based on emerging data.
The dose level will not exceed 40 mg LSF oral solution (1mg/ml) per day.</td></tr>
</table>

	If, within a treatment group, any of the following occurs, dose escalation will be stopped: Safety stopping criteria • There is 1 or more serious adverse event, considered to be related to emodepside; • 2 or more subjects who present any severe adverse event considered to be related to emodepside If a cohort fulfils a dose escalation stopping criterion, that dose level will not be repeated. PK stopping criteria • predicted mean plasma concentrations in the subjects at the next scheduled dose level exceed or equal: C_{max} 634 µg/L, $AUC_{(0-24)}$ 6,025 µg·h/L (based on the NOAEL level in dog toxicology studies, exposures resulting from 4 weeks of treatment at 10 mg/kg/d) The scheduled dose of emodepside may be reduced if, for example, the results of safety tests give any cause for concern, or tolerability is poor. If adverse events occur that cause mild or moderate discomfort but do not in any way threaten the health of the subject, that dose level may be repeated with the aim of exploring further the relationship between dose and adverse event. If, in the judgement of the Safety Review Group (SRG), it would not be reasonable to expose further subjects to the level of discomfort experienced by the subjects who have already received the dose, the next scheduled dose may be reduced. The reduction may be either to one of the dose levels that has already been given, or to an intermediate level that has not previously been given; in either case, the aim is to learn more about the relationship between adverse event and dose (or plasma concentration) of drug.
Sample Size	Up to 24 healthy male subjects (not including replacement subjects), in up to 3 cohorts, of 8 subjects.
Statistics	No formal statistical sample size estimation has been performed for this, due to the exploratory nature of this study. 6 subjects per dose level (cohort) is considered sufficient to examine the safety and tolerability of emodepside as well as the pharmacokinetics after single and multiple doses. However, 8 subjects will be recruited per group to ensure a minimum of 6 evaluable subjects complete the study. One or two formal interim analyses may be performed. **Safety:** Safety and tolerability data will be summarized using the Safety Population. Safety and tolerability data will be summarized using the following parameters: • Vital signs; • 12-lead ECG;

- Haematology;
- Clinical chemistry;
- Coagulation;
- Urinalysis;
- Physical and neurological examination;
- Ophthalmology assessments
- AEs.

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

Pharmacodynamic:

PD data will be summarized using the Safety Population. PD variables at each planned assessment, and change in PD variables from baseline at each planned post baseline assessment, will be summarised by actual treatment.

Pharmacokinetic:

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

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

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

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

Table 1- Schedule of events (once-daily dosing)

Study Procedure	Screen		In-Patient Phase																																									
	Visit 1	Visit 2	Pre-dosing Period															First dosing day													Dosing Period													
Day ± allowable deviation	-28 to -2		-3	-2				–1										0													1				2	3	4	5	6	7	8			
Subject information and Informed Consent	X																																											
Medical history (including demographics and previous / concomitant medications)	X																																											
Physical examination[b]	X																																											
Neurological examination	X																																											
Ward Admission			X																																									
Urine drugs of abuse and alcohol breath test	X		X																																									
Ophthalmological examination		X																																										
Hours[a] (pre/post drug)			-60	-48	-47	-46	-44	-24	-23.5	-23	-22.5	-22	-21	-20	-18	-16	-12	0*	0.25	0.5	1	1.5	2	2.5	3	4	6	8	12	15	0*	1	2	4	0*	0*	0*	0*	0*	0*	0*	1	2	4
Oral glucose tolerance test (OGTT)[d]				X	X	X	X																								X	X	X	X							X	X	X	X
Glucose, Insulin, Glucagon, and Cortisol profiles								X		X		X		X			X	X			X		X			X			X		X													
Administration of study medication[e]																		X													X				X	X	X	X	X	X	X			
12-lead safety ECG[f]	X							X[f]	X	X	X	X	X	X		X	X	X[f]		X	X	X	X		X	X		X	X		X				X	X	X	X	X	X	X			
Vital signs[g]	X							X	X	X	X	X	X	X		X	X	X		X	X	X	X		X	X		X	X		X				X	X	X	X	X	X	X			
Adverse event monitoring[h]	X		X	X				X		X		X	X	X	X	X	X	X			X		X		X	X	X	X	X		X				X	X	X	X	X	X	X			
PK and metabolites in plasma																		X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X			
Laboratory Safety[i]	X[i]							X										X													X							X[j]			X			
Short neurological and physical examination[b,k]								X[b,k]		X[k]		X[k]		X[k]			X[k]	X[k]			X[k]		X[k]			X[k]			X[k]		X[k]				X[k]	X	X	X	X	X	X			

Study Procedure	**In-Patient Phase**																			**Out-Patient Phase**				**Follow-Up**
	Last dosing day													**Evaluation Period**										
Day ± allowable deviation	**9**													**10**		11	**12**	**13**	**14**	**17** ±2	**20** ±2	**23** ±2	**27** ±2	**30** ±2
Hours [a] (pre/post drug)	**0***	**0.25**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**15**	**24**	**36**	**48**	**72**	**96**	**120**					
Glucose, Insulin, Glucagon, and Cortisol profiles	X			X		X			X			X		X		X[c]	X[c]	X[c]	X[c]					X
Administration of emodepside[e]	X																							
12-lead safety ECG[f]	X[e]		X	X	X	X		X	X		X	X		X			X		X					X
Vital signs[g]	X			X	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring[h]	X		X	X		X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
PK and metabolites in plasma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Safety[i]	X													X					X			X[j]		X
Short neurological and physical examination[b,k]	X[k]		X	X[k]		X[k]			X[k]			X[k]		X[k]		X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X
Ophthalmological examination[l]														X										

* = assessments will be pre-dose

[a]: Including a 10-minute supine rest before supine BP, HR, and ECG; and also recommended before drawing blood samples

[b]: Height and weight at screening, for calculation of BMI; only weight (no height) at –24h (Day –1)

[c]: Samples will be taken after subjects have been fasting

[d]: Glucose and insulin profiles only at these timepoints

[e]: Administration of study drug while fasting. Study medication will be given at approximately the same time each morning (±15 mins).

[f]: To include triplicate ECGs at these timepoints, with about 1 minute between each recording; single recordings at all other timepoints

[g]: Vital signs to include supine BP and HR. Oral temperature only at screening and -24h (Day –1)

[h]: Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety; however, at these indicated timepoints will be scheduled questioning about AEs using non-leading questions (eg, “how are you feeling?”)

[i]: Haematology, Coagulation, Chemistry; Urinalysis by dipstick; to include, at screening only, HIV 1, 2, Hepatitis B, C, HbA1c

[j]: A reduced laboratory safety panel will be used at these timepoints

[k]: Abbreviated neurological and physical examinations

[l]: Additional ophthalmological examinations will be performed where clinically indicated.

Table 2- Schedule of events (twice-daily dosing)

Study Procedure	**Screen**		**In-Patient Phase**																																						
	Visit 1	**Visit 2**	**Pre-dosing Period**															**First dosing day**													**Dosing Period**											
Day ± allowable deviation	**-28 to -2**		**-3**	**-2**				**–1**										**0**													**1**				**2**	**3**	**4**	**5**	**6**	**7**	**8**			
Subject information and Informed Consent	X																																								
Medical history (including demographics and previous / concomitant medications)	X																																								
Physical examination[b]	X																																								
Neurological examination	X																																								
Ward Admission			X																																						
Urine drugs of abuse and alcohol breath test	X		X																																						
Ophthalmological examination		X																																							
Hours[a] (pre/post drug)			**-60**	**-48**	**-47**	**-46**	**-44**	**-24**	**-23.5**	**-23**	**-22.5**	**-22**	**-21**	**-20**	**-18**	**-16**	**-12**	**0***	**0.25**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12***	**15**	**0***	**1**	**2**	**4**	**0***	**0***	**0***	**0***	**0***	**0***	**0***	**1**	**2**	**4**
Oral glucose tolerance test (OGTT)[d]				X	X	X	X																							X	X	X	X							X	X	X	X
Glucose, Insulin, Glucagon, and Cortisol profiles								X		X		X		X			X	X			X		X			X			X	X													
Administration of study medication[e]																		X								X				X				X	X	X	X	X	X	X			
12-lead safety ECG[f]	X							X[f]	X	X	X	X	X	X		X	X	X[f]		X	X	X	X		X	X		X	X		X				X	X	X	X	X	X	X			
Vital signs[g]	X							X	X	X	X	X	X	X		X	X	X		X	X	X	X		X	X		X	X		X				X	X	X	X	X	X	X			
Adverse event monitoring[h]	X		X	X				X		X		X	X	X	X	X	X	X			X		X		X	X	X	X	X		X				X	X	X	X	X	X	X			
PK and metabolites in plasma																		X	X	X	X	X	X	X	X	X	X	X	X	X		X				X	X	X	X	X	X	X			
Laboratory Safety[i]	X[i]							X										X												X							X[j]			X			
Short neurological and physical examination[b,k]								X[b,k]		X[k]		X[k]		X[k]			X[k]	X[k]			X[k]		X[k]			X[k]			X[k]		X[k]				X[k]	X	X	X	X	X	X			

Study Procedure	**In-Patient Phase**																			**Out-Patient Phase**				**Follow-Up**
	Last dosing day													**Evaluation Period**										
Day ± allowable deviation	**9**													**10**		11	**12**	**13**	**14**	**17** ±2	**20** ±2	**23** ±2	**27** ±2	**30** ±2
Hours [a] (pre/post drug)	**0***	**0.25**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**6**	**8**	**12**	**15**	**24**	**36**	**48**	**72**	**96**	**120**					
Glucose, Insulin, Glucagon, and Cortisol profiles	X			X		X			X			X		X		X[c]	X[c]	X[c]	X[c]					X
Administration of emodepside[e]	X																							
12-lead safety ECG[f]	X[e]		X	X	X	X		X	X		X	X		X			X		X					X
Vital signs[g]	X			X	X	X		X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Adverse event monitoring[h]	X		X	X		X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
PK and metabolites in plasma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Safety[i]	X													X					X			X[j]		X
Short neurological and physical examination[b,k]	X[k]		X	X[k]		X[k]			X[k]			X[k]		X[k]		X[k]	X[k]	X[k]	X	X[k]	X[k]	X[k]	X[k]	X
Ophthalmological examination[l]														X										

* = assessments will be pre-dose

[a]: Including a 10-minute supine rest before supine BP, HR, and ECG; and also recommended before drawing blood samples

[b]: Height and weight at screening, for calculation of BMI; only weight (no height) at –24h (Day –1)

[c]: Samples will be taken after subjects have been fasting

[d]: Glucose and insulin profiles only at these timepoints

[e]: Administration of study medication. Study medication will be given at approximately 12h intervals, at the same time each morning and evening (±15 mins)

[f]: To include triplicate ECGs at these timepoints, with about 1 minute between each recording; single recordings at all other timepoints

[g]: Vital signs to include supine BP and HR. Oral temperature only at screening and -24h (Day –1)

[h]: Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety; however, at these indicated timepoints will be scheduled questioning about AEs using non-leading questions (eg, “how are you feeling?”)

[i]: Haematology, Coagulation, Chemistry; Urinalysis by dipstick; to include, at screening only, HIV 1, 2, Hepatitis B, C, HbA1c

[j]: A reduced laboratory safety panel will be used at these timepoints

[k]: Abbreviated neurological and physical examinations

[l]: Additional ophthalmological examinations will be performed where clinically indicated.

Planning Information

Study Timelines

Final protocol available	August 2017
Study treatment supply available	September 2017
FSFV	Q3 2018
Duration of recruitment period	
Duration of follow-up period (if applicable)	
LSLV	
Interim analysis	
Final study report	

STUDY SCOPE

Target countries	United Kingdom
Enrollment target	Randomisation: Up to 24 subjects (excluding replacements) Screening: based on anticipated screen failure rate of 50% - approx. 48 subjects
Number of site(s)	1
Number of subjects per site	(see enrolment target)
DSMB involvement	A safety review will be performed before each dose escalation.
Partners involvement	The study will be conducted by Hammersmith Medicines Research, a Contract Research Organisation (CRO) specialized in the conduct of Phase I trials. The CRO will be contracted for all core study-related activities (eg data management, monitoring, PK analysis, statistical analysis, writing final study report).
Other study special needs	Not applicable

Study Treatments Supply

Study treatments	1) Emodepside Liquid Service Formulation (LSF) solution (1mg/ml) 2) Matching placebo solution for emodepside LSF solution (1mg/ml) Storage conditions for solution (active and placebo): Store at 2°C-8°C. Upright storage. Supplied by Bayer, packaged and labelled by Creapharm (France)
Labeling instructions	TBC
Other information	N/A

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. Okoye, I. C. & Onwuliri, C. O. Epidemiology and psycho-social aspects of onchocercal skin diseases in northeastern Nigeria. *Filaria J.* **6,** 15 (2007).

6. Amazigo, U. O. Detrimental effects of onchocerciasis on marriage age and breast-feeding. *Trop. Geogr. Med.* **46,** 322–325 (1994).

7. 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).

8. WHO. Working to overcome the global impact of neglected diseases - summary - First WHO report on neglected tropical diseases. (2010).

9. 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).

10. 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).

11. 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).

12. Meredith, S. E. & Dull, H. B. Onchocerciasis: The First Decade of Mectizan™ Treatment. *Parasitol. Today* **14,** 472–474 (1998).

13. Fobi, G. *et al.* Managing the Fight against Onchocerciasis in Africa: APOC Experience. *PLoS Negl. Trop. Dis.* **9,** e0003542 (2015).

14. 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).

15. 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).

16. Zahner *et al.* Filaricidal efficacy of anthelmintically active cyclodepsipeptides. *Int J Parasitol.* **31***,* 1515-22 (2001).

17. 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).

18. Willson, *et al.* The effect of the anthelmintic emodepside at the neuromuscular junction of the parasitic nematode Ascaris suum. *Parasitology* **126**, 79-86 (2003).

19. 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).