DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL SYNOPSIS

A Phase 1, Relative Bioavailability Study to Investigate the Pharmacokinetics of new IR-tablet Formulations compared to Oral Solution and Food Effect, as well as Safety and Tolerability of Emodepside (BAY 44-4400), in a Randomized, Open-labelled, Parallel-Group Design after Single Oral Dosing in Healthy Male Subjects

Name of product(s)	Emodepside (BAY 44-4400)
Drug Class	Anthelmintic octadepsipeptide
Phase	1 relative bioavailability and food effect study
Indication	Treatment of onchocerciasis (river blindness) and potentially other filarial diseases, including lymphatic filariasis
Protocol Number	DNDI-EMO-03
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SAC approval	Not required
Clinical Trial Protocol Synopsis Version / Date	Version: 1.0 / 31 July 2017

SYNOPSIS

Background Information	**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 affect the adult worms, providing 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 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 perpetual 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*[5]. 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, which kills *O. volvulus* adult worms, for use 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.
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 relative bioavailability study, pharmacokinetic as well as safety and tolerability of 2 new formulations of emodepside given as single dose 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.

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

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. <u>General Pre-Clinical Summary</u>

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 receiving 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 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 down to 50%, 25%, 12.5% and 6.25% respectively. 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. The relative bioavailability of the first tablet formulation was about 35% for 5 mg and about 12% for 20 mg compared to the LSF solution. Due to the low bioavailability of these IR tablet formulations, they will not be used in further studies. There was no report of clinically significant abnormalities in any laboratory parameters. Nevertheless, 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 clinically significant abnormalities in vital signs, electrocardiogram (ECG) parameters or physical examination throughout the study, regardless of the formulation. Data of cohort 10 are still under evaluation, 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 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 pharmacokinetics of two new emodepside (BAY 44-4400) immediate release (IR)-tablet formulations in comparison to the liquid service formulation (LSF). Part A is performed in a 5-group parallel design. A single 5 mg oral LSF dose will be compared to a 5-mg tablet of formulation #406 and a 5 mg tablet of formulation #416 under fasted conditions and a 5 mg tablet of formulation #406 and a 5 mg tablet of formulation #416, administered after a high calorie and high fat meal. Part B is performed in a 1 or 2 arm parallel design. 2 tablets of formulation #406 (5 mg strength) and/or 2 tablets of formulation #416 under fasted condition may be tested. The decision on part B and the selection of formulation will be done after the availability and evaluation of the kinetic results of part A. One group in this parallel design will consist of 12 healthy male

	Caucasian subjects. **Secondary Objectives:** To investigate and compare safety and tolerability of emodepside after single doses of 5 mg and 2 x 5 mg after oral administration in healthy subjects.
Trial Endpoints	**Primary Endpoints** **PK Variables for the relative bioavailability study given as single dose:** For investigation of pharmacokinetics plasma concentrations of emodepside, they will be determined at the times given in the Trial Flow Chart. Based on the serum concentration time data (collected after administration of single drug administration), the following PK parameters of emodepside will be calculated: • The primary PK parameter is $AUC_{(0\text{-}7days)}$/D • Main PK parameters are: $AUC_{(0\text{-}7days)}$, $AUC_{(0\text{-}7days)}$/D, Cmax , Cmax/D • Exploratory pharmacokinetic parameters are: AUC(0-tn), AUCnorm, Cmax,norm, t1/2, tmax, MRT Other parameters: AUC(tn-∞), points terminal **Secondary Endpoints** **Safety and Tolerability Variables:** • Adverse Events (AEs), • Vital signs (HR and BP, weight, BMI), • 12-lead ECG (HR, PR, QRSD, QT/QTcF), will be analysed at hoc for safety and for the final data base and report by central reading • Clinical laboratory parameters (haematology: leucocytes, erythrocytes, haemoglobin, haematocrit, MCV, MCH, MCHC, platelets, reticulocytes, WBC, coagulation: PTT, prothrombin time; biochemistry: AST, ALT, AP, GGT, LAP, LDH, CK, amylase, lipase, CHE, glucose, cholesterol [HDL, LDL, total], triglycerides, creatinine, urea, uric acid, bilirubin [total and conjugated], total protein, sodium, potassium, calcium, chloride and magnesium in serum; urinalysis: by dip stick).
Trial Design	This will be a relative bioavailability study in a single-centre, open-label, randomized, parallel-group design, investigating in part A five treatments (A, B, C, D, E) given as single oral-doses. In part B two treatments (F, G) will be investigated. The study will evaluate PK of a single dose of emodepside of two new IR-tablet formulations #406 and #416 in comparison to the oral liquid formulation and in comparison of tablets given with food. Also, safety and tolerability will be evaluated. Both tablets are immediate release (IR) dosage forms with rapid dissolution under in vitro test conditions.

	Emodepside coated tablet #406 contains granules of emodepside and the polymer hypromellose acetate succinate as a solid dispersion to enhance solubility. Tablets contain the active substance emodepside, hypromellose acetate succinate, macrogol 15 hydroxystearate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate. The tablets are film-coated with a coating composed of hypromellose, macrogol, ferric oxide red, and titanium dioxide. Tablet formulation #406 is expected to disintegrate in the acid milieu of the stomach and the resultant granules to dissolve rapidly in the upper intestine. Emodepside coated tablet #416 contains granules of emodepside and the polymer copovidone as a solid dispersion to enhance solubility. Tablets contain the active substance emodepside, copovidone, macrogol 15 hydroxystearate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate. They are film-coated with a coating composed of hypromellose, macrogol, ferric oxide red, and titanium dioxide. Tablet formulation #416 is expected to disintegrate in the acid milieu of the stomach and the resultant granules to dissolve rapidly in the stomach and upper intestine. The two tablet formulations (#406 and #416) are identical in appearance. They both are round, pink coated tablets with a diameter of 5 mm. Tablets are packaged in HDPE bottles with a desiccant capsule inside each bottle and the bottles are closed with child-resistant PP screw cap closures with induction seal. The study will be performed in a single site specialized in Phase 1 studies. For each subject the study starts with the Screening Visit, which can be up to about 3 weeks before the profile day (dosing). For eligible subjects, admission to the ward will be at latest the evening before the profile day. A short physical examination, adverse event and concomitant medication checks, blood pressure, alcohol breath tests and DOA testing will be done. At the profile day (0d00), subjects will receive a single dose of emodepside in the morning either fasted or given with food, followed by an in-house observation period of 3 days after the last administration of the test substance. Subjects will be discharged from the study ward 3 days after the administration of test substance provided there are no medical objections. An out-patient follow-up period of additional 4 days with blood samples in the morning will follow. The follow-up visit will be performed 7 days after drug administration. The total duration of the in-house period will be 4 days and 4 nights. See also Study Schedule of Events for detailed study procedures.
Rationale for Trial Design	The study is performed in a randomized, open label, parallel group design. The PK analyses are performed in an unblinded way as well as the safety analyses by the medical responsible of the sponsor. Emodepside has during the first 24 hours a very short half-life for a single dose. After 3, 7, 16 and 47 hours the maximum plasma concentration is reduced down to 50%, 25%, 12.5% and 6.25% respectively.

	But the terminal half-life is about 523 hours. The rationale for the parallel group design instead of the standard cross-over design is the terminal half-life of Emodepside of about 523 hours, which is anticipated to interfere with a cross-over design. This long half-life also requires pharmacokinetic blood samples during the outpatient period up to 168 hours = 7 days. The Follow-Up Visit is scheduled 7 days after the last study drug administration according to standard practice for this type of study.
Main Entry Criteria	**Inclusion:** • Healthy male white/Caucasian subjects • 18 to 45 years of age • Normal body weight range (BMI between 18 and 30 kg/m^2) • Able to understand and follow instructions • Able to participate in the study for the entire period • Signed written informed consent. **Exclusion:** • Participation in another clinical trial within 3 months prior the study • Abnormal findings in medical history at Screening • Donation of more than 100 mL of blood within 4 weeks prior or blood donation of approximately 500 mL within 3 months prior to Screening • History of relevant diseases of vital organs, of the central nervous system or other organs (e.g. diabetes mellitus, liver diseases, seizures, etc.) • Subjects with a medical or psychiatric disorder, condition or history of such that would increase the risk associated with study participation, or impair the subject's ability to participate or complete this study, in the opinion of the investigator or the sponsor • Febrile illness within 1 week before the start of the study • Subjects with a history of severe allergies, non-allergic drug reactions, or multiple drug allergies • Subjects with a hypersensitivity to the investigational drug, the control agent and/ or to inactive constituents • Regular daily consumption of more than 21 units of alcohol per week, or 3 units per day. • Regular daily consumption of more than one liter of xanthin-containing beverages • Regular daily consumption of more than 25 cigarettes • Regular use of therapeutic or recreational drugs • Use of medication within the 2 weeks preceding the study which could interfere with the investigational product

	• Relevant deviation from the normal range in the clinical examination • Relevant deviation from the normal range in clinical chemistry, haematology or urinalysis • Resting heart rate in the awake subject below 50 BPM or above 90 BPM • Systolic blood pressure below 100 mmHg or above 145 mmHg • Diastolic blood pressure above 95 mmHg • Relevant pathological changes in the ECG such as a second or third-degree AV block, prolongation of the QRS complex over 120 msec or of the QT / QTc-interval (B and F) over 450 msec • Subjects testing positive in the drug screening • Excluded therapies which may impact on the interpretation of study results (e.g. physiotherapy, etc) Subjects will be advised they must avoid excessive physical training in a gymnasium 48 h before screening until the final Follow-Up visit.
Removal of subjects from study	A subject who discontinues the study for any reason before dosing with study medication is defined as a Withdrawal. A subject who discontinues participation in the study prematurely after at least one dose of study medication was administered is defined as a Dropout. Subjects who drop out may be replaced in case the number of drop-outs per cohort exceeds 2.
Safety Review	Safety of this single dose study will be reviewed on a continuous basis
Study Duration	For each subject, the study starts with a screening visit up to approximately 3 weeks before the single-dose administration of emodepside, and ends with the follow-up visit 7 days after the last dosing.
Rationale for Selection of Dose and Route for Administration	**Rationale for Dose Selection** The study drug and doses given in part A of this relative bioavailability study are 5 mg oral solution (LSF), a 5 mg IR-tablet of two new formulations in fasting conditions and the 5 mg IR-tablet given with food, in form of a high calorie and high fat meal. In part B, depending on the results of part A, the two new formulations will be administered and tested given as 2x5mg tablets. In the single ascending dose escalation study DNDI-EMO-001, the 5 and 10 mg oral solution was tested and proven to be safe and well tolerated. The maximum single dose which was proven to be safe and tolerated is 20 mg BAY 44-4400 (oral solution), resulting in an exposure of AUC 1,926 $\pm$ 300 ng*h/mL (CV% of 15.6) and Cmax 316 $\pm$ 88 ng/mL (CV% of 27.7). The 10-mg dose of the LSF resulted in a Cmax of 179 ng/mL. Therefore, a single dose of 5 mg oral solution and as well a 5-mg tablet and 2 x 5 mg tablets are safe and justified. The maximum single dose tested is 40 mg emodepside OD, resulting in an

	exposure of AUC 4,315 ± 1623 ng*h/mL (CV% of 37.6) and Cmax 612 ± 139 ng/mL (CV% of 22.8). This dose was estimated as safe but not well tolerated and following observations have been made: • 5 subjects reported at least one non-serious treatment emergent adverse effects (TEAEs), including 4 subjects who experienced blurred vision and 2 who reported visual impairment. In addition, 2 subjects reported dizziness and 1 reported headache. All AEs were mild in severity and resolved spontaneously in absence of treatment. Also, 6 subjects had pre-prandial fasting glucose plasma levels above 5.8 mmol/L for at least 2h after dosing and 5 had insulin levels below 13 pmol/L. Glucagon, cortisol and leptin variations did not show any particular trend. • In addition, in cohort 10 (data are still under evaluation), 28 non-serious adverse events (AEs) were reported after administration of 40 mg LSF, 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 and 1 some concomitant sense of imbalance. Also, 1 subject reported tongue paraesthesia that lasted for approximately 6 hours. The exposure and pharmacokinetic data observed in the single dose escalation study DND-EMO-001 suggest a dose-proportional increase in AUC (107 ± 39 ng*h/mL after 1 mg to 4315 ± 1623 ng*h/mL after 40 mg emodepside) and Cmax (18.9 ± 3.8 ng/mL after 1 mg to 612 ± 139 ng/mL after 40 mg emodepside) and Tmax of approximately 1 h. The 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 down to 50%, 25%, 12.5% and 6.25% respectively. But the terminal half-life ($t_{1/2, 0-\infty}$) is calculated to be around 523 hours. Variability in plasma exposure was estimated to be moderate to low.
Rationale for Study Population	This Phase I study will be performed in 12 healthy, male volunteers per group aged 18 to 45 years. For ease of recruitment in the location of the Phase I unit, only Caucasian subjects will be recruited to avoid unexpected high variability.
Sample Size:	The study is planned for 7 groups with a single dose treatment with 12 subjects per group, in total 84 subjects.

Study Treatments	**Test-Drug:** Emodepside new immediate release (IR) tablets of 5 mg or oral liquid formulation. **Formulations to be tested:** **Part 1:** *Part 1.1* • Treatment A: 5 mg oral liquid formulation, fasted; 12 subjects • Treatment B: 5 mg IR-tablet formulation #406, fasted; 12 subjects • Treatment C: 5 mg IR-tablet formulation #416, fasted; 12 subjects *Part 1.2* • Treatment D: 5 mg IR-tablet formulation #406, given with a high calorie high fat meal 12 subjects • Treatment E: 5 mg IR-tablet formulation #416, given with a high calorie high fat meal 12 subjects **Part 2:** • Cohort 6: 2 x 5 mg IR-tablet formulation #406 (treatment F), fasted; 12 subjects • Cohort 7: 2 x 5 mg IR-tablet formulation #416 (treatment G), fasted; 12 subjects Route of administration: oral Time and frequency of administration: Approximately 8 – 9 am for the first subject, tablet to be taken either fasting or with food (treatments D and E).
Statistics Sample size Randomization	For this relative bioavailability study in a 5 plus 2 groups, parallel group design, with an exploratory character, a sample size of 12 subjects per treatment group is considered sufficient to examine the pharmacokinetic properties of the new IR-tablet formulation in comparison to the oral liquid formulation after a single dose with oral administration of the investigational drug. Safety and tolerability of emodepside will be investigated as well. For evaluation, a minimum number of 10 evaluable subjects per group is required for those treatment groups which are decided, based on kinetic parameters for full evaluation. Subjects who drop out of the study will be replaced in case the number of withdrawals exceeds 2 subjects per group. All subjects who received at least one dose of the trial medication will be included in the evaluation of safety and in pharmacokinetics if at least valid plasma samples up to 72h are available. For further details see the study flow chart. Statistical analysis will be performed using SAS® 9.3 or later on a Windows PC. All data will be listed and trial summary tables will be provided. The primary variable to determine the oral bioavailability of the two new IR-

	tablet formulations and its potential food effect is $AUC_{(0\text{-}7days)}$/D of Emodepside (BAY 44-4400). **Demographic and other baseline characteristics** Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented. Frequency tables for qualitative data will be provided. **Adverse events** Individual listings of adverse events (including age, weight, height, gender, adverse event as reported, start, duration, severity, relation to study drug) will be provided. The incidence of treatment-emergent adverse events will be summarized by treatment using MedDRA preferred terms grouped by primary system organ class. **Safety:** Quantitative data (e.g. data of haematology, blood chemistry, vital signs, ECG parameters) will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by treatment for the original data as well as for the differences versus baseline. Frequency tables for qualitative data will be provided. Clinical laboratory values outside reference range will be highlighted with "L" for low and "H" for high. Additional tables with abnormal values will be presented. Graphical displays of individual data as well as mean values with standard deviations will be included (vital signs, ECG). **Pharmacokinetic parameters and evaluation:** The concentration-time course of all analytes will be summarized separated for each treatment. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the limit of quantification (LOQ). For the calculation of the mean value a data point below LOQ will be substituted by one half of this limit. In tables showing mean values, where values below LOQ are included in the calculation of mean values, these means will be marked. Individual and mean plasma-concentration vs. time curves will be plotted by treatment using both linear and semi-logarithmic scale. Pharmacokinetic characteristics (tmax excluded) will be summarized by the statistics mentioned above. tmax and points terminal will be described utilizing minimum, maximum and median as well as frequency counts. To assess the relative bioavailability and the effect of food, analysis of variance (ANOVA) models will be fitted to the tablet and solution data with the logarithm of the pharmacokinetic parameters $AUC_{(0\text{-}7days)}$/D and Cmax/D as the dependent variable, with formulation and fed/fasted as a fixed effect.

	Based on these analyses point estimates (LS-Means) and 90% confidence intervals for the ratios “B / A”, “C / A”, “F/A”, “G/A”, “D/B” and “E/C” will be calculated in part A. In addition, “F/A” and “G/A” in part B. The acceptance range 80-125% will be applied for the assessment of the relative bioavailability and the potential food effect. To assess dose proportionality, exploratory ANOVA models will be fitted to the relevant fasted data in parts A and B with the logarithm of the pharmacokinetic parameters $AUC_{(0\text{-}7days)}$ and Cmax as the dependent variables and dose as a fixed effect. Based on these analyses point estimates (LS-Means) and 90% confidence intervals for the ratios will be calculated.

Appendices

Screening visit

	pre-study visit		
Subject information	X		
Informed consent	X		
Medical history incl. previous and concomitant medications	X		
Smoking status	X		
Physical examination	X		
Neurological examination	X		
Supine phase, 15 minutes before ECG & blood pressure	X		
Blood pressure, heart rate	X		
12 lead ECG	X		
Clinical chemistry	X		
Haematology and coagulation	X		
Urinalysis	X		
Drug screening	X		
HIV, Hepatitis B, C	X		

Study flow chart and / or schedule procedure

Profile day, Study time 0d00h00m through 0d23h00m (profile day)
Treatments A, B, C and F, G under fasted conditions, treatments D and E 5 minutes after intake of food

Time (d)	-00	00	00	00	00	00	00	00	00	00	00	00	00	00		
Time (h)	00	00	00	00	01	01	02	02	03	04	05	06	08	12		
Time (min)	30	00	15	30	00	30	00	30	00	00	00	00	00	00		
In-house period	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Meals (a: for treatments D & E)	Xa										X		X	X		
Administration of study drug (Emodepside)		X														
Supine phase, 15 minutes before activity		X		X	X	X	X	X	X	X		X	X	X		
Adverse event questioning		X			X		X		X	X			X	X		
Blood pressure, heart rate		X		X	X	X	X		X	X			X	X		
12 lead ECG		X		X	X	X	X		X	X			X	X		
Clinical chemistry, haematology and coagulation		X														
Urinalysis		X														
Pharmacokinetic blood sampling		X	X	X	X	X	X	X	X	X		X	X	X		

Meals on the profile day 0d:
Lunch 5h, snack 8h and dinner 12 hours after the 8am
The corresponding measurements or procedures in the morning will be done fasted and before drug intake

Study time 1d00h00m through 7d00h00m of each treatment

Time (d)	01	01	02	03	05	07
Time (h)	00	12	00	00	00	00
Time (min)	00	00	00	00	00	00
In-house period	→		→	→		
Out-patient period					→	→
Supine phase, 15 minutes before activity	X	X	X	X	X	X
Adverse event questioning	X	X	X	X	X	X
Neurological and short physical examination	X	X	X	X	X	X
Blood pressure, heart rate	X	X	X	X	X	X
12 lead ECG	X		X	X	X	X
Clinical chemistry and haematology	X		X	X	X	X
Urinalysis	X		X	X	X	X
Pharmacokinetic blood sampling	X	X	X	X	X	X
Discharge from ward				X		
Follow-up visit						X

Meals on days 1d to 7d will be:
Breakfast after morning procedures and measurements
Lunch 5h, snack 8h and dinner 12 hours after the 8am
The corresponding measurements or procedures in the morning will be done fasted

Follow-up visit. (7 days after the last study drug intake)

Time (d) Time (h) Time (min)	Follow up visit
Adverse events	X
Physical examination Neurological examination	X
Supine phase, 15 minutes before ECG & RR	X
Blood pressure, heart rate	X
ECG	X
Clinical chemistry and hematology	X
Urinalysis	X
Pharmacokinetic sample	X

Trial flow chart details:

In-house period:	-0d12 to 3d
Meals on study days:	0d05, 0d08, 0d12 after the corresponding measurements or procedures
Caffeine:	0d08
Smoking:	0d08
Sequence of measurements:	ECG, HR, BP, AEs, kinetics, other laboratory parameters

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Planning Information

Study Timelines

Final protocol available	July 2017 latest
Study treatment supply available	LSF Solution ready to be shipped end June 2017* 5mg Tablets ready to be shipped June 2017* *Shipment will not occur until CTA approval and QP release
FSFV	
Duration of recruitment period	
Duration of follow-up period (if applicable)	
LSLV	Q4 2017 (also contingent on length of follow-up determined by PK results as detailed in protocol)
Interim analysis	n/a
Final study report	

****Provisional dates, these can be finalized after CRO (and thereby country) selection

STUDY SCOPE

Target countries	One site to be selected
Enrollment target	Randomisation: 60 subjects in part A plus 2 x 12 subjects in part B Screening: based on anticipated screen failure rate of 50% - approx. 144 subjects
Number of sites	1
Number of subjects per site	(see enrolment target)
DSMB involvement	A safety review will be performed before each dose escalation step.
Partners involvement	The study will be conducted by one Contract Research Organisation specialized in the conduct of Phase I trials. The CRO will be contracted for all core study-related activities (e.g. data management, monitoring, PK analysis, statistical analysis, writing final study report). The selection of the CRO is pending.
Other study special needs	No specialist equipment needed. The PK assay method will be transferred to the CRO. A double-print out of ECGs will be prepared so that central reading is possible.

Study Treatments Supply

Study treatments	1) Emodepside tablets 5 mg formulation #406 2) Emodepside tablets 5 mg formulation #416 3) Emodepside Liquid Service Formulation 1 mg/mL Storage conditions: Do not store above 25°C, Do not freeze. (to be checked) Supplied by Bayer, packaged and labelled by Creapharm (France)
Labeling instructions	Draft label. See attachment embedded
Other information	n/a