1 Synopsis

Title	A Phase-II, Randomised, Double-blind, Parallel-group Trial to Investigate Emodepside (BAY 44-4400) in Subjects with *Onchocerca volvulus* Infection, comprising: Part 1 to Investigate Safety, Tolerability, Pharmacodynamics, Pharmacokinetics, and Dose-Response Relationship for Efficacy (Proof-of-Concept); Part 2 to Investigate Efficacy of Selected Doses, Safety, Tolerability and Pharmacokinetics
Short Title	Emodepside Phase-II Trial for Treatment of Onchocerciasis
Clinical Phase	Phase II
Investigational centres	Multicentre
Study Design	The overall objective of the study is to determine the safety and efficacy of emodepside in subjects infected with *Onchocerca volvulus*. To reach this objective, the study is divided into several parts: Part 1 Proof of Concept: Investigation of safety in mf-positive subjects and of dose-response relationship for efficacy, i.e. proof of concept, for emodepside and placebo at 12 months. Part 1 is divided into three consecutive sub-parts: • Part 0 Pilot Group: single dose of emodepside to verify the exposure in the African study population and in both sexes. Open label, no control • Part 1a Safety: single and multiple doses of emodepside in mf-positive subjects of both sexes, stratified by low or high mf loads. Randomised, double blind, parallel group, placebo controlled. • Part 1b Dose Response: dose-response relationship with four dose regimens of emodepside to select up to two suitable dose regimens for subsequent evaluation in Part 2. Randomised, double-blind, parallel group, placebo controlled. Part 2 Regimen Selection: Investigation of superiority of up to two dose regimens of emodepside as compared to ivermectin at 24 months. Randomised, double blind, double dummy, parallel group, ivermectin controlled.
Study Objectives	The primary objectives are to determine: Part 0: Pilot Group

	The safety and tolerability of emodepside in *O. volvulus* infected subjects Part 1: Dose Response A dose-range of emodepside that will sterilise the adult female worm and/or have a macrofilaricidal effect at Month 12 Co-Primary objective: the effect of emodepside on skin microfilariae at Month 12. Part 2: Regimen Selection Whether emodepside effectively eliminates microfilariae from the skin at 24 months after treatment
Investigational medicinal product	Emodepside
Name of active substance	Emodepside
Dose and Duration of Treatment	Part 0 Pilot Group (fasting): - Group 0: 15 mg emodepside IR tablet OD for 1 day, low mf load Part 1a Safety (fasting): - Group A 30 mg emodepside IR tablet OD 1 day or placebo, low mf load - Group B 30 mg emodepside IR tablet OD 1 day or placebo, high mf load - Group C 15 mg emodepside IR tablet OD 7 days or placebo, low mf load - Group D 15 mg emodepside IR tablet OD 7 days or placebo, high mf load Part 1b Dose Response (fasting): - 30 mg emodepside IR tablet OD 1 day, or placebo - 15 mg emodepside IR tablet OD 7 days, or placebo - 15 mg emodepside IR tablet OD 14 days, or placebo - 15 mg emodepside IR tablet BID. 10 days, or placebo Part 2 Regimen Selection (fasting): - Regimen 1 of emodepside IR tablet to be selected from Part 1, or ivermectin - Regimen 2 of emodepside IR tablet to be selected from Part 1, or ivermectin
Route of Administration	Oral
Indication	Onchocerciasis

Inclusion and Exclusion Criteria	Note: This is a summary of the main Inclusion and Exclusion Criteria, please refer to the full protocol for the full Criteria. *Inclusion* 1. Written, signed (or thumb-printed) and dated informed consent 2. Men and women 18 to 65 years of age with *Onchocerca volvulus* infection a. Presence of at least 1 excisable subcutaneous nodule/onchocercoma detected on palpation b. *O. volvulus* infection diagnosed by skin snip method, documented skin assessment on 4 skin snips. c. Body weight at Screening ≥ 40 kg 3. For women of child-bearing potential (WOCBP), acceptance of the requirement to use a highly effective form of birth control *Exclusion* 1. Administration of medication or herbal therapies as follows: i. The following antifilarial therapies or medication that may have an antifilarial effect: • ivermectin, ≤ 6 months prior to IMP administration, and / or • doxycycline, ≤ 1 year prior to IMP administration, more than 2 weeks course, and / or • moxidectin, ≤ 2 years prior to IMP administration. ii. Other preventive chemotherapy, e.g. as part of an MDA programme within 14 days prior to IMP administration. 2. Presence of any clinically significant medical condition at Screening: including, but not limited to diabetes type 1 or 2; past or current history of neurological or neuropsychiatric disease or epilepsy; sickle cell disease; known human immunodeficiency virus (HIV) infection, disclosed by review of medical history or concomitant medication. 3. Presence of abnormal physical findings or laboratory values at Screening that could interfere with the objectives of the trial or the safety of the subject, in the opinion of the Investigator. 4. Known hypersensitivity to any ingredient of the IMP, including the active ingredient emodepside, or to ivermectin, or to any medication used during the study. 5. Current hyperreactive onchodermatitis or severe manifestations due to onchocerciasis.

	6. Coincidental infection with other endemic filarial parasites based on laboratory tests at Screening (*Wuchereria bancrofti*, *Mansonella* spp.). 7. Coincidental infection with *Loa loa* based on medical history or positive test at Screening. 8. In groups intended to include subjects without ocular involvement: ocular microfilariae or onchocercal eye lesions, assessed at Screening. 9. Ophthalmological history or conditions that could make the ocular examination difficult or represent a risk for the safety of the subject. 10. For WOCBP: Pregnancy or breastfeeding
Safety Review Committee	A Safety Review Committee (SRC) will be appointed with a minimum of three Sponsor representatives, including at least one medically qualified person, and the Investigator. SRC decisions will be executed only if the Data and Safety Monitoring Board (DSMB) concur.
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board (DSMB) will be established by the Sponsor. The DSMB will review and evaluate, at intervals and as defined in the DSMB charter: the progress, scientific validity and data integrity of a clinical trial, the safety data and critical efficacy variables collected during the trial to recommend to the Sponsor to continue, modify or terminate the trial.
Number of Subjects	Part 0: 8 subjects of both sexes Parts 1a and 1b: 150 subjects of both sexes Part 2: 420 subjects of both sexes
Safety and Tolerability and Primary Efficacy Endpoints	The safety and tolerability endpoints are: • AE assessment (all reported AEs); • physical, skin, and neurological examination findings; • vital signs; • 12-lead ECG; • clinical laboratory parameters: haematology, coagulation, biochemistry, urine analysis; • ophthalmological examination findings. The primary efficacy endpoints are: Part 1: Dose Response • Absence (or presence) of live female adult worms with normal embryogenesis (assessed by histological examination of nodules collected on nodulectomy at Month 12).

	• Co-Primary endpoint: Absence (or presence) of skin microfilariae across four skin snips sampled at Month 12. Part 2: Regimen Selection • Absence (or presence) of skin microfilariae at Month 24, assessed across four skin snips in a subject.
Time-points of measurement for primary variables	Month 4 (Part 0) Month 12 (Part 1a and Part 1b) Month 24 (Part 2)
Sample size determination	**Part 0/1a:** Statistical sample size was not derived from a power calculation due to the exploratory nature of the safety evaluation, which is the primary objective of the study. The sample size is therefore the size commonly used in Phase-I safety assessments. **Part 1b:** Because the aim of the study is to assess the effect of emodepside on macrofilariae and microfilariae, both effects will be estimated with no hierarchy of importance in the Dose Response step. 1) Assuming a rate of success, i.e. no microfilariae across 4 skin snips, of 10% for placebo, 15% for the low dose regimen, 38% for the medium dose regimen, 50% for the medium/high dose and 60% for the high dose, the power of the trend test (K ordered independent binomials) reaches 99.9% with 30 subjects per group at Month 12. If such a success rate is applicable to placebo then the power of the comparison of placebo with the best dose (response rate of 60%) exceeds 99 %. 2) Assuming that 40% of subjects will have no live females with normal embryogenesis in the placebo group, 60% in the low dose regimen, 70% in the medium dose, 80% in the medium/high dose regimen and 90% in the high dose, the power with 30 subjects per group reaches 99% (alpha = 0.025 one-sided). **Part 2:** Dose finding will be based on the comparison of the ivermectin group with each of the two dose regimens selected. The primary endpoint will be the absence of microfilariae across four snips sampled at Month 24. Sample size calculation is based on the primary analysis of microfilariae. Based on modelling of a macro- and microfilaricidal compound with a hypothetical macrofilaricidal efficacy of 75% and on a conservative efficacy at Month 24 of emodepside with a success rate of 40% and a success rate of 20 % for ivermectin (expectations obtained by simulations), using a Bonferroni adjustment for the two comparisons (conservative adjustment) and consequently a two-sided type one error of 0.025, retaining an exact power of 80% and a conditional test of superiority (likelihood ratio test), the required sample size per arm

	is 139 subjects (rounded to 140) receiving at least one dose of randomized treatment (mITT) (based on StatXact software).
Statistical analyses	**Part 0/1a:** Because the sample size is limited, most of statistical analyses will be descriptive with a presentation of results by arm, i.e. total dose. **Part 1b:** Because the aim of the study is to assess the effect of emodepside on macrofilariae and microfilariae, both effects will be estimated with no hierarchy of importance in the Dose Response step. The main analysis for the two effects will test the dose-response relationship using the four dose regimens for emodepside and placebo. The success rate for each planned total exposure will then be presented graphically and the best doses selected. The absence (or presence) of microfilariae across four skin snips sampled at Month 12 will be used as an estimand. A trend test for clustered (site) data will be applied for the dose response relationship (StatXact). **Part 2:** The primary statistical approach is Steingrimsson's approach with the use of logistic regression to adjust the probability of success of each subject on microfilarial load at baseline or another indicator of the response detected in Part 1 and resampling to estimate the magnitude of the treatment effect (excess rate) and its alpha-adjusted confidence interval. With this approach, an overall excess rate can be estimated even if there is an interaction between strata (microfilarial load or other) and treatment. This approach may be modified once the results of Part 1 are available, for example if microfilarial load at baseline had no effect). The two primary comparisons of the proportion of subjects with no microfilaria across four skin snips will be: emodepside high dose versus ivermectin and emodepside low dose versus ivermectin. The ascending Hochberg procedure will be used to cope with the issue of multiplicity, i.e. two dose regimens versus active control.