DNDi
Drugs for Neglected Diseases *initiative*

CLINICAL TRIAL PROTOCOL

A Phase-II, Randomised, Double-blind, Parallel-group, Proof-of-concept Trial to Investigate ABBV-4083 given for 7 or 14 Days or in Combination with Albendazole in Subjects with *Onchocerca volvulus* Infection, comprising:

Part 1 to Investigate Safety, Tolerability, Efficacy for Dose-Ranging and Pharmacokinetics;

Part 2 to Investigate Efficacy of Selected Doses, Safety, Tolerability and Pharmacokinetics

Short title	Tylamac phase II trial for treatment of onchocerciasis
Name of product	Chemical Name: Tylosin, 4^B *O*-[(4-fluorophenyl)methyl] Associated name: ABBV-4083
Drug Class	Macrolide
Phase	II
Indication	Treatment of onchocerciasis (river blindness)
Trial Protocol Number	AbbVie Protocol B18-894 / **DNDi-TYL-01**
Sponsor	DND*i*, Chemin Camille-Vidart, 15, 1202 Geneva, Switzerland
Trial Protocol Version/Date	Version 2.0 dated 09 November 2021
Protocol Amendment Number/Date	Amendment 1 dated 09 November 2021
Registry number	ClinicalTrials.gov identifier: NCT04913610 Pan African Clinical Trials Registry: PACTR202104600961505

Contact Details

TRIAL SPONSOR

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- **Sponsor's Medical Expert (24 Hours)**

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- **Clinical Project Managers**

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DND*i* DND*i*
Chemin Camille-Vidart, 15, 1202 Geneva, Switzerland
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- **Serious Adverse Event (SAE) Reporting**

Sponsor contact details for SAE reporting
DNDi Clinical Team, e-mail: SAETYL01study@dndi.org

(See Section 9.3.4.8 for full details)

INSTITUTION:

PNLMTN- CTP will ensure the preparation and management of the clinical trial sites as well as the conduct and coordination of the clinical trial in DRC sites.

PNLMTN-CTP
Avenue de la Justice N°36 , Commune de la Gombe
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The full list of contacts involved in this clinical trial including the clinical sites can be found in the clinical trial contact list.

Sponsor Signatures

I have read and approved this protocol. My signature, in conjunction with the signatures of the Investigators, confirms the agreement of the Sponsor and Investigator that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

Signature of the Sponsor's Medical Responsible

The signatory agrees to the content of the final clinical study protocol as presented.

Name: Dr. [redacted] MD Role: [redacted]

Date: ..... Signature:

Signature of the Sponsor's Clinical Manager

The signatory agrees to the content of the final clinical study protocol as presented.

Name: [redacted] MSc Role: [redacted]

Date: ..... Signature:

Signature of the Sponsor's Head of Clinical Program

The signatory agrees to the content of the final clinical study protocol as presented.

Name: [redacted] PhD, PD Role: [redacted]

Date: ..... Signature:

Signature of the Sponsor's Statistician

The signatory agrees to the content of the final clinical study protocol as presented.

Name: [redacted] PhD, on behalf of DNDi

Role: [redacted]

Date: 10-Nov-2021

Signature: [redacted]

Investigator Signature

I have read this protocol and agree that it contains all information necessary to carry out the study. I will conduct the study as described herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the Investigational Medicinal Product and the conduct of the study.

I will use only the Informed Consent Forms approved by the Sponsor or its representative and the Ethics Committee(s) and (where applicable) the Regulatory Authority, and will fulfil all responsibilities for submitting pertinent information to the Ethics Committee (EC) responsible for the study if required by national law.

I agree that the Sponsor or its representatives, and respective Ethics Committee(s) and Regulatory Authorities shall have access to any source documents from which case report form information may have been generated.

I agree that the study will be conducted in accordance with all applicable laws and regulations, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the Sponsor's study file and in the Investigator Site File at the investigational centre.

In the protocol document, this page may remain unsigned.

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Protocol Amendment 1 rationale

The Sponsor considers that with this amendment the overall risk-benefit assessment for the protocol remains unchanged. Also the changes below do not impact the determination of the sample size, nor the integrity of the trial design. In addition, there is no impact on subjects already enrolled in the study at the time of protocol amendment, nor consequences for the evaluation of the study results.

The first participants were prescreened, screened and started treatment in May 2021. At the time of writing this amendment, a total of 272 participants were prescreened, 125 screened and 57 randomised into the study. The screen failure rate was over 50% at the time of this amendment and the main reasons for screen failure were co-infection with other filarial species (*Mansonella perstans* and/or *Wuchereria bancrofti)* and the presence of THC in urine.

The prevalence of other filarial species in the patient population was unknown prior to the start of the study due to lack of disease mapping. The consequences of killing intracellular endosymbionts (*Wolbachia*) using antibiotics has been very well described. Doxycycline, given at a dose of 200 mg daily for 4 to 6 weeks, has been shown to decrease the development, embryogenesis, fertility, and viability of filarial worms in species that harbor *Wolbachia*[1]. This is also the case for *Wuchereria bancrofti*[2,3] and *Mansonella perstans*[4,5] infection. Due to the indirect mode of action, i.e. killing of *Wolbachia* endobacteria, mf decline slowly over the course of approximately 12 months and thus no parasite-induced adverse events are expected in patients coinfected with other *Wolbachia*-harbouring filaria, as is the case for onchocerciasis. Therefore, we aim to include subjects with coinfections with *Wuchereria bancrofti* or *Mansonella spp.*

Furthermore new criteria for re-screening have been added. These measures will give additional opportunities for subjects who already went through intensive screening procedures to participate, reduce the number of screen-failures, and to optimise recruitment.

In addition, during the screening of the subjects, it was observed that the number of screening procedures was challenging within the allocated protocol window for the operational site team. Therefore, it was decided to allow more flexibility for the screening window.

Some editorial changes were also implemented in this amendment to add clarity or correct some inconsistencies. Some administrative changes have also been made.

Overall rationale for the amendment:

1. Administrative and editorial changes
2. Remove the exclusion criterion regarding the co-infection with *Mansonella* species and *Wuchereria Bancrofti*
3. Add criteria for re-screening to optimise recruitment, without compromising safety
4. Clarify that only abnormal and clinically significant ECGs and urine analyses would require re-test or further evaluations
5. Remove non-critical tests/assessments to reduce burden for sites
6. Clarify that future research could also be done on other parasites

7. Allow more time for repeat testing to avoid unnecessary blood draw after agreement from the sponsor
8. Fix some inconsistencies or add clarification for some procedures

Details about the changes and rationale are reported in below table.

Section # and Name	Description of Change	Brief Rationale
Title Page and Contact Details	Update of DNDi's Switzerland contact details at several places.	The street name of DNDi's office in Geneva has changed on 01Mar2021 due to a motion made to the Geneva Canton in 2019 accepting to change 100 street names from masculine to feminine.
Sponsor Signatures	Removal of Medical Director (retain the Medical Responsible) as signatory and update of the Trial Statistician contact.	Per DNDi SOP, the Medical Director is not required to sign in addition to the Medical Responsible. Change of Trial Statistician.
1 Synopsis	Correction of Kimpese' site name	Correct error
	Correction of typographical error in the inclusion criterion about body weight (should be ≥ 40kg).	This is a correction in the synopsis to be aligned with section 6.1
1 Synopsis and Section 6.2 Exclusion Criteria	Clarification that only clinically significant abnormal physical examination or laboratory findings would exclude a subject from the study.	All abnormal results are not necessarily clinically significant and therefore this criterion is clarified.
	Removal of co-infection with *Mansonella* species and *Wuchereria bancrofti* as exclusion criterion.	Refer to Protocol amendment rationale section above. No risk is foreseen for subjects with co-infection with other filarial worms.
	Clarification that exclusion criteria 7.viii regarding the presence of more than 50 microfilariae in the anterior segment corresponds to number of microfilariae in one eye.	Clarification only.
	Extension of the washout period for alcohol use (2 days versus 24 hours) and of drugs	Alcohol use can be tested up to 48 hours before the first IMP administration as the participants will already be on site and this will allow more

	of abuse (15 days versus 24 hours)	flexibility on the organizational aspects at the site. As re-screening will now be allowed in certain circumstances for participants screen-failing on drugs of abuse (see section 6.5.1 below), the washout period has been extended to avoid potential drug-drug interactions.
3.5.4 Risks Associated with Epidemics	Clarification that COVID-19 tests may be performed on site personnel and/or study subjects if required by standard clinical care.	Protect the study subjects in case of suspicion of COVID-19 infection and apply standard of care.
6.5.1 Screening Failure	Clarification that screening failures refer to subjects who discontinue study participation prematurely after they have signed the study **main** informed consent form (ICF) and undergone screening assessments and that subjects who re-enter the screening process must sign a new **main** ICF.	Clarification only due to the use in the study of 2 Informed Consents Forms: 1 pre-screening ICF and 1 main ICF.
	Clarification that up to 2 re-screenings are allowed	To give the opportunity to participants who already went through intensive screening procedures to be re-screened
	Allowance of re-screening for subjects who screen-failed due to blood donation/transfusion, vaccinations, recent alcohol or drugs consumption, if agreed by the investigator and sponsor.	On a case-by-case basis to give more possibility for subjects who already went through screening to participate, and to optimise recruitment, whilst respecting the wash-out period required to ensure safety of participants.
7.4.2 Unblinding Measures	Addition of more details about the procedure in event of emergency unblinding by the Investigator, including the precautions to prevent unnecessary unblinding of subjects, Sponsor personnel, and additional Site personnel.	Clarification.

9.2.2 Screening Period	Clarification that initial screening procedures that are still within the protocol window do not need to be repeated in case of re-screening.	This amendment will avoid unnecessary repeated procedures such as additional blood draw for the participants.
9.3.3.1.1 Blood, Urine and Skin Snip Parasitology and Appendices 1 and 2 (Tables 7 and 8)	Removal of *Schistosoma haematobium* testing at screening.	Change to symptom-directed assessment for *Schistosoma haematobium* at screening to avoid unnecessary procedures. Based on the mode of action, ABBV-4083 is not expected to be efficacious in patients with schistosomiasis.
9.3.3.8 Standard 12-lead ECG	Clarification that clinically significant abnormality will be checked by repeat ECG.	An abnormal ECG might not be clinically significant. This amendment will avoid unnecessary repeat testing.
9.3.3.9.1 Haematology, Biochemistry, Urinalysis and Urine Microscopy	Requirement for urine microscopy to be conducted only if the abnormal urinalysis results were clinically significant.	A urinalysis might be abnormal but this may not be clinically significant (e.g. red blood cells in the urine of a menstruating female). This has been amended to avoid unnecessary analysis and conduct urine microscopy only if clinically significant.
9.3.3.9.3 Pregnancy Tests	Specification that pregnancy test must be highly sensitive. Allowance for repeat pregnancy tests to be highly sensitive urine upon sponsor's approval.	To add precision. To avoid unnecessary blood draw.
9.3.4.4 Eliciting Adverse Event Information	Addition that end date will also be recorded in the eCRF for non-serious AEs. Addition that the adverse event start and stop times are to be recorded when available during the In-house period	This was omitted previously This would allow to more easily identify and capture Treatment Emergent Adverse Event (TEAE).
9.3.4.5 Adverse Event Reporting Period	Added the precision 'treatment emergent' AE regarding the AE reporting period.	Clarification.
9.3.4.6 Grading of Adverse Event Severity	Removed bicarbonate, and lactate dehydrogenase (LDH).	Correction for consistency with Appendix 5. Laboratory analyses. These 2 parameters are not required in the study for safety monitoring and were not present in the list of laboratory analyses, nor in the study operational manual.

9.3.4.10 Adverse Event Follow-up	Removal of the categories needed to document outcome of an AE.	Information that need to be recorded in the eCRF for AEs is detailed in section 9.3.4.4. No need to have further details as the lists of possible action taken and outcome are present on the SAE form and AE eCRF page.
10.2 Analysis Sets	Clarification added: per protocol population includes ITT subjects who had **live** female adult worms at the Month 6 nodulectomy.	This change was implemented to align with the SAP
10.10 Interim Analysis of Part 2 and DSMB Recommendation for Phase III	Correction that details on the analysis and method are described in the SAP and not in the DSMB charter	This correction was implemented to align with the SAP/DSMB charter.
Appendices 1 and 2 (Tables 7and 8)	Allowance of a longer period for repeat testing at screening in exceptional circumstances upon sponsor's approval. With the exception of pregnancy testing which must be repeated within 2 days and can be a highly sensitive urine test if serum test was already done.	The repeat testing 2-day window was initially only set for organizational purposes, however it was noted that this window is too short for the site personnel and agree to extend it to 3 days (and more, if required, in exceptional circumstances, upon approval from the sponsor) to avoid another blood draw, as this has no impact on the safety of the participants and data analysis.
	Change from 'urinary cannabis screen' to 'urinary drug screen.	For consistency with section below: Appendix 5 Laboratory analyses, Parameters of laboratory analyses
	Clarifications provided in some of the footnotes	For better clarity and alignment with changes done in the protocol.
Appendices 5. Laboratory analyses-Parameters of laboratory analyses	Removal of creatinine clearance as eGFR only is being used.	Correction only. Creatinine clearance was not listed in the laboratory parameters elsewhere in the protocol.
	Revision of the Urine Drugs Screen section to specify Drugs of Abuse Screen.	For consistency of wording with the exclusion criteria regarding drugs of abuse, and reflecting the RDT in use.

References used in the Protocol Amendment 1 rationale:

1. Hoerauf, A., et al., *Wolbachia endobacteria depletion by doxycycline as antifilarial therapy has macrofilaricidal activity in onchocerciasis: a randomized placebo-controlled study.* Med Microbiol Immunol, 2008. **197**(3): p. 295-311.
2. Taylor, M.J., et al., *Macrofilaricidal activity after doxycycline treatment of Wuchereria bancrofti: adouble-blind, randomised placebo-controlled trial.* Lancet, 2005. **365**(9477): p. 2116-21.
3. Taylor, M.J., et al., *Anti-Wolbachia drug discovery and development: safe macrofilaricides for onchocerciasis and lymphatic filariasis.* Parasitology, 2013: p. 1-9.
4. Coulibaly, Y.I., et al., *A randomized trial of doxycycline for Mansonella perstans infection.* N Engl J Med, 2009. **361**(15): p. 1448-58.
5. Batsa Debrah, L., et al., *The Efficacy of Doxycycline Treatment on Mansonella perstans Infection: An Open-Label, Randomized Trial in Ghana.* Am J Trop Med Hyg, 2019. **101**(1): p. 84-92.

1 Synopsis

Title	A Phase-II, Randomised, Double-blind, Parallel-group, Proof-of-concept Trial to Investigate ABBV-4083 given for 7 or 14 Days or in Combination with Albendazole in Subjects with *Onchocerca volvulus* Infection, comprising: Part 1 to Investigate Safety, Tolerability, Efficacy for Dose-Ranging and Pharmacokinetics; Part 2 to Investigate Efficacy of Selected Doses, Safety, Tolerability and Pharmacokinetics
Short Title	Tylamac phase-II trial for treatment of onchocerciasis
Protocol number	DNDi-TYL-01/ AbbVie Protocol B18-894
Clinical Study Phase	Phase II
Investigational Centres	Hôpital Général de Référence de Masi-Manimba, Kwilu, Democratic Republic of Congo Centre de Santé de Référence de Kimpese, Kongo central, Democratic Republic of Congo Additional centres may be included.
Study Design	Multicentre, randomised, active and/or placebo-controlled, double-blind, parallel-group, adaptive Phase-II study in two parts: Part 1 will use a surrogate endpoint of *Wolbachia* depletion in adult female worms to: • establish proof-of-concept for ABBV-4083 in onchocerciasis by demonstrating superiority of the regimens of ABBV-4083 alone over the control regimen, albendazole alone, which has been shown to have little or no activity in onchocerciasis, • establish the activity of ABBV-4083 and albendazole in combination by demonstrating superiority of a regimen of ABBV-4083 plus albendazole over regimens of ABBV-4083 and albendazole alone of equal duration, and • establish up to two preferred regimens of ABBV-4083 and/or ABBV-4083 + albendazole to progress into Part 2 of the study. Part 2 will use a clinically relevant endpoint of depletion of skin microfilaria at Month 24 to: • identify the preferred regimen of ABBV-4083 or ABBV-4083 + albendazole to progress into Phase III trials. • evaluate the effect of a dose of ivermectin 6 months after ABBV-4083 or ABBV-4083 + albendazole on skin microfilarial density at Months 12, 18 and 24. If the superiority of ABBV-4083 + albendazole over ABBV-4083 alone is not demonstrated in Part 1, surrogate endpoint data from Part 2 (i.e. *Wolbachia* depletion in adult worms at Month 6) from Arms with ABBV-4083 + albendazole and ABBV-4083 alone will be combined with data from Part 1 to assess the superiority of ABBV-4083 + albendazole to ABBV-4083 alone (Part 2 Alternate Scenario).
Study Objectives	**Primary Objectives** *Part 1:* • To determine whether treatment with ABBV-4083 or ABBV-4083 + albendazole effectively depletes *Wolbachia* bacteria in adult female worms at Month 6 by immunohistology; • To establish the superiority of ABBV-4083 + albendazole to each drug alone

	according to the depletion of Wolbachia bacteria in adult female worms at Month 6 by immunohistology. *Part 2:* • To determine whether treatment with ABBV-4083 or ABBV-4083 + albendazole effectively eliminates microfilariae from the skin at 24 months; • If superiority of 7-day treatment with ABBV-4083 + albendazole to 7 days of ABBV-4083 is not established in Part 1, the Alternate Scenario of Part 2 (see Section 3.3) has the additional objective to establish that a combination of ABBV-4083 + albendazole is superior to ABBV-4083 alone by combining data from Parts 1 and 2. **Key Secondary Objectives** *Part 2:* • To determine whether ABBV-4083 or ABBV-4083 + albendazole demonstrates a macrofilaricidal effect at 24 months; • To determine whether ABBV-4083 or ABBV-4083 + albendazole inhibits embryogenesis in adult female worms at 24 months.
Investigational Medicinal Products	*Part 1* **Names of active substances**: ABBV-4083 (Tylamac) Albendazole (Zentel) **Dose and Duration of Treatment**: • Arm A (N = 30): 7 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 matching placebo • Arm B (N = 30): 7 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 400 mg • Arm C (N = 30): 7 days of ABBV-4083 400 mg + albendazole 400 mg followed by 7 days of ABBV-4083 matching placebo • Arm D (N = 30): 3 days of ABBV-4083 400 mg + albendazole 400 mg followed by 4 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 matching placebo • Arm E (N = 30): 7 days of ABBV-4083 matching placebo + albendazole 400 mg followed by 7 days of ABBV-4083 matching placebo **Route of Administration:** Oral *Part 2* **Names of active substances**: ABBV-4083 (Tylamac) Albendazole (Zentel) Ivermectin (Stromectol) **Dose and Duration of Treatment**: • Arm K (n = 84): initial treatment with an active regimen selected from Part 1, followed by ivermectin at Month 6; • Arm L (n = 84): initial treatment with the same active regimen selected from Part 1 as Arm K, followed by ivermectin matching placebo at Month 6; • Arm M (n = 84): initial treatment with a second active regimen selected from Part 1, followed by either ivermectin or ivermectin matching placebo at Month 6; • Base scenario - Arm N1 (n = 42): initial treatment with ABBV-4083 matching placebo and albendazole matching placebo, followed by ivermectin at Month 6. • Alternate scenario - Arm N2 (n = 84): 7 days of ABBV-4083 400

	mg plus appropriate duration of albendazole matching placebo and ABBV-4083 matching placebo followed by either ivermectin or ivermectin matching placebo at Month 6. Ivermectin at Month 6 will be administered at the standard single oral dose of 150 µg/kg body weight. **Route of Administration:** Oral
Indication	Onchocerciasis
Inclusion and Exclusion Criteria	The Inclusion and Exclusion Criteria are the same for Parts 1 and 2. **Inclusion Criteria** 1. Written, signed (or thumb-printed) and dated informed consent, after having the opportunity to discuss the study with the Investigator or a delegate. 2. Men and women with Onchocerca volvulus infection, 18 to 65 years of age inclusive at time of Screening: i. Presence of at least one excisable subcutaneous nodule/ onchocercoma detected on palpation; ii. *O. volvulus* infection diagnosed by skin snip method: documented mf-positivity on skin assessment on at least 2 out of 4 skin snips. 3. Body weight ≥ 40 kg at Screening. 4. For women of child-bearing potential, acceptance of the requirement to use a highly effective form of birth control from Day 0 until at least 1 month after the final intake of IMP (Part 1: day 43; Part 2: 1 month after the administration of ivermectin or matching placebo at the Month 6 visit). Choice of birth control method must be clearly documented. **Exclusion Criteria** 1. Participation in any studies other than purely observational studies within 3 months prior to Screening, or during the trial, or within 5 times the half-life of the drug tested in the previous clinical trial or is currently in the follow-up period for any clinical trial. 2. Any vaccination within 4 weeks prior to IMP administration. 3. Acute infection and/or febrile illness requiring therapy within 14 days prior to IMP administration. 4. Administration of medication or herbal preparations as follows: i. Administration of any medication (with the exception of diclofenac, paracetamol, ibuprofen and aspirin) or herbal preparation within 14 days prior to IMP administration; ii. Use of strong CYP3A inhibitors or inducers including but not limited to ritonavir, ketoconazole, rifampicin, phenytoin, phenobarbital, carbamazepine, cimetidine within 14 days or 10 half-lives, whichever is longer, prior to IMP administration; iii. Use of other drugs known to interact with albendazole i.e. praziquantel, theophylline or dexamethasone, within 14 days or 10 half-lives, whichever is longer, prior to IMP administration; iv. The following antifilarial therapies, or medication that may have an antifilarial effect: o ivermectin; ≤ 6 months prior to IMP administration; and/or o doxycycline, ≤ 1 year prior to IMP administration: more than 2-week course; and/or o any other anti-Wolbachia treatments i.e. minocycline, rifapentine or rifampicin, ≤ 1 year prior to IMP administration: more than 2-week course; and/or o moxidectin, ≤ 2 years prior to IMP administration.

	v. Other preventive chemotherapy, e.g. as part of an MDA programme, within 14 days prior to IMP administration 5. Requirement for and inability to avoid ivermectin during the first 6 months after IMP administration. Requirement for albendazole during the first 28 days after IMP administration or more than one dose per year thereafter given in MDA. 6. Presence of any of the following at Screening, that could interfere with the objectives of the trial or the safety of the subject, in the opinion of the Investigator: i. Clinically significant abnormal physical examination or laboratory findings; ii. Any clinically significant medical condition, including, but not limited to significant acute or chronic liver or kidney condition or cardiovascular disease, active infection, current or previous epilepsy, known human immunodeficiency virus infection, disclosed by review of medical history or concomitant medication. 7. Ophthalmological history or conditions that could interfere with the objectives of the trial or compromise the safety of the subject in the opinion of the Investigator, assessed at Screening, including the following (subject will be excluded if any of the criteria are met for either eye): i. Inflammatory eye disease, glaucoma, severe uveitis; evidence of retinal cysticercosis; ii. History of surgery for glaucoma; iii. Severe keratitis, and/or cataracts that interfere with visualisation of the posterior segment of the eye; iv. Evidence of an increased risk of acute glaucoma, based on examination of anterior chamber; v. Evidence of ocular media opacity, including lens opacity and vitreous opacities, that make difficult ocular examination in the opinion of the investigator; vi. Evidence of retinal or optic nerve pathology, including age-related macular degeneration; vii. Severe visual impairment (best corrected or pinhole visual acuity worse than 6/60 metres), severe reduction of peripheral visual fields (greater than grade 3 on Frequency Doubling Technology) or blindness; viii. Any microfilariae identified in the posterior segment of the eye or more than 50 microfilariae in the anterior segment of one eye. 8. History of drug or alcohol abuse within 6 months prior to IMP administration. 9. Use of alcohol within 48 hours and/or use of drugs of abuse within 15 days before IMP administration. 10. Clinically significant history of cardiac abnormality, and/or relevant pathological abnormalities in the ECG in the screening period, such as atrioventricular block (PR interval > 240 msec), or prolongation of the QRS complex > 120 msec or QTcF interval > 450 msec. 11. Abnormal laboratory test results at Screening, defined as: i. Aspartate aminotransferase/serum glutamic oxaloacetic transaminase and/or alanine aminotransferase/serum glutamic pyruvic transaminase > 2 x upper limit of normal (ULN) and/or total bilirubin > 1.5 x ULN; ii. Serum potassium < lower limit of normal; iii. Serum creatinine > ULN and estimated glomerular filtration rate < 60 mL/min (using the Modification of Diet in Renal Disease equation) 12. History of severe drug allergy, non-allergic drug reactions, severe adverse reaction to any drug, or multiple drug allergies.

	13. Known hypersensitivity to any ingredient of the IMPs, including the active ingredient of ABBV-4083, macrolides, albendazole or to ivermectin or to any medication used during the study (e.g. for eye examination). 14. Blood donation within 8 weeks prior to Screening or blood transfusion received within 1 year prior to Screening. 15. Coincidental infection with high *Loa loa* load (> 8000 microfilariae/mL) at Screening. 16. Current hyperreactive onchodermatitis or severe manifestation due to onchocerciasis. 17. Any other past or current condition that the Investigator feels would exclude the subject from the study or place the subject at undue risk. 18. For women of child-bearing potential: pregnant, based on date of last menstrual period, and pregnancy test prior to first intake of IMP, or breastfeeding. 19. Unwilling or unable to comply with the requirements of the study protocol for the entire duration of the study, in the opinion of the Investigator. 20. Unable to participate in the study as per local law, if applicable.
Type of Control	In part 1: active control: albendazole In Part 2, base scenario: placebo control In Part 2, alternate scenario: active control: ABBV-4083
Study Duration	In Part 1: each subject's participation will last approximately 6½ months, excluding the screening period, which may be up to 8 weeks. In Part 2: each subject's participation will last approximately 24½ months, excluding the screening period, which may be up to 8 weeks.
Data and Safety Monitoring Board	An independent Data and Safety Monitoring Board will be established by the Sponsor in accordance with ICH guidelines. The composition, roles and responsibilities of the DSMB will be described in detail in the DSMB charter.
Number of Subjects	150 subjects in Part 1 294 subjects (base scenario) or 336 subjects (alternative scenario) in Part 2
Primary Endpoints and Time-points for Measurement of Primary Endpoints	The primary efficacy endpoints are: *Part 1:* • the status of each live female adult worm as without *Wolbachia* endobacteria or not, as assessed by immunohistology of nodules collected after nodulectomy at 6 months; *Part 2:* • the status of each subject as without skin microfilariae or not at 24 months, assessed across all skin snips in each subject.
Sample Size Calculation	*Part 1:* For the primary hypothesis in Part 1 that compares the proportion of live female adult worms without *Wolbachia* at Month 6 between a single-drug ABBV-4083 arm and the albendazole arm, an alternating logistic regression will be used to compare the endpoint between two arms, taking into account the clustering of this worm-level endpoint by subject. 17 subjects per arm will provide 88% power to detect the difference between a single-drug ABBV-4083 arm where 70% of worms are without *Wolbachia* and the albendazole arm where 30% of worms are without *Wolbachia* (2-sided α =0.10). For the primary hypothesis in Part 1 that compares the proportion of live female adult worms without *Wolbachia* at Month 6 between the combination arm of ABBV-4083 + albendazole for 7 days and the single-drug ABBV-4083 arm, 25 subjects per arm will provide 81% power to detect the difference between the combination arm, where 90% of worms are without *Wolbachia*,

	and the single-drug arm, where 70% of worms are without *Wolbachia*, with a 2-sided α-level of 0.10 using alternating logistic regression. 30 subjects will be enrolled per arm to account for 17% drop out by Month 6. *Part 2:* For the Part 2 primary hypothesis in the base scenario that compares the proportion of subjects without skin microfilariae at Month 24 between an active arm (Arm K, L or M) and the placebo arm (Arm N1), 62 subjects in the active arm and 31 subjects in the placebo arm will provide 91% power to detect the difference between an active arm (Arm K, L or M) where 70% of subjects are without skin microfilariae at Month 24 and the placebo arm (Arm N1) where 30% of subjects are without microfilariae at Month 24, using a logistic regression with 2-sided α=0.017 accounting for multiplicity adjustment. Assuming a 25% drop-out rate by Month 24, 84 subjects in each active arm and 42 subjects in the placebo arm are planned to be enrolled.
Statistical Analyses	All safety analyses will be performed on the Safety Population, which consists of all subjects who received at least one dose of IMP. Safety will be assessed by AEs, laboratory tests, vital signs, and ECG variables. This will be descriptive. *Part 1:* The Part 1 primary and combination endpoints, the proportion of adult female worms without *Wolbachia* endobacteria assessed by immunohistology at 6 months, will be summarised among the PP for ND6M population, and the odds ratio for each of the treatment arm comparisons of interest (Arm A vs E and Arm B vs E; Arm C vs E, Arm C vs A, Arm D vs E, Arm D vs A) will be calculated using contrasts within an alternating logistic regression model with treatment arm as factor and also accounting for within-subject correlation, each at 2-sided $\alpha = 0.10$. Part 2: The Part 2 primary endpoint of the percentage of subjects without skin microfilariae at Month 24 will be summarised across the PP for microfilariae population, and the adjusted odds ratio for each of the 3 active treatment arms will be compared to the comparator arm (Arm K vs N1 or N2, Arm L vs N1 or N2, and Arm M vs N1 or N2) using contrasts within a logistic regression model with treatment arm as factor and number of sites per subject (1, > 1) and mean baseline mf (≤ 5, > 5) as covariates at 2-sided $\alpha = 0.017$ Supportive subgroup analyses for the primary endpoint will also be performed for at least the following subgroups: number of sites per subject (1, > 1) and mean baseline mf (≤ 5, > 5).

List of Abbreviations

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALCOA	attributable, legible, contemporaneous, original, accurate
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APOC	African Program for Onchocerciasis Control
AST	aspartate aminotransferase
AUC	area under the curve
AWOL	Anti-Wolbachia Consortium
BCRP	breast cancer resistance protein
bw	body weight
CD1	cluster of differentiation 1
CL	clearance
Cl^-	chloride
C_{max}	maximum concentration in blood
C_{min}	minimum concentration in blood
CNS	central nervous system
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DALY	disability-adjusted life years
DCF	data clarification form
DNA	deoxyribonucleic acid
DND*i*	Drug for Neglected Diseases *initiative*
DSMB	Data and Safety Monitoring Board
EC_{50}	half maximal effective concentration
EC_{90}	90% effective concentration
ECG	electrocardiogram/electrocardiography
eCRF	electronic case report form
FDA	Food and Drug Administration
FE	food effect
FIH	first in human
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice

hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
IC_{50}	concentration required to inhibit 50% of organisms
ICC	intraclass correlation coefficient
ICF	informed consent form
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IR	immediate release
IRB	institutional review board
IRT	interactive response technology
ITT	intention to treat
IVM	ivermectin
LSF	liquid service formulation
M	metabolite
MAD	multiple ascending dose
MATE	multidrug and toxin extrusion protein
MDA	mass drug administration
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
mf	microfilaria/microfilariae
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
ND24M	nodulectomy at 24 months
ND6M	nodulectomy at 6 months
NK_1	neurokinin 1
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OATP	organic anion transporting polypeptide
OCP	Onchocerciasis Control Program
OCT	organic cation transporter
P-gp	glycoprotein P
PCR	polymerase chain reaction
PD	pharmacodynamic
PIG-a	phosphatidyl inositolglycan class A gene
PK	pharmacokinetic
PoC	proof of concept
PP	per protocol
QD	once daily

RDT	rapid diagnostic test
SAD	single ascending dose
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TaNT	test-and-not-treat
TEAE	treatment-emergent adverse event
t_{max}	time to reach maximum concentration in blood
TNT	test and treat
TylA	tylosin A
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	women of child-bearing potential

2 Introduction

2.1 Background Information on Onchocerciasis

Onchocerciasis represents a major public health problem in affected countries with up to 1.34 million disability adjusted life years lost in 2017.[1] This disproportionately high number is driven by disease-induced disability, and overall loss of economic productivity. The challenge for mass drug administration (MDA) programs is to eliminate transmission by periodic treatment of vulnerable populations with ivermectin. This removes microfilariae (mf) from the skin and temporarily prevents the release of mf by the adult female worm. However, mf return within 6-8 months, and control strategies delivering ivermectin on a six or 12 monthly cycle must be maintained over a 10 to 15-year period to reach elimination. Notably, MDA requires extensive logistical efforts and financial commitments. Treating entire populations requires ethical discussions and evaluations of cost-effectiveness. Success in MDA is dependent on the sustained coordination of supply logistics to ensure that treatment reaches all target recipients. Because of these challenges, interruption of transmission and disease elimination worldwide has proven more difficult than initially projected. In addition, MDA given for long periods carries the risk of resistance, described for ivermectin use in animal-health applications, together with sub-optimal response in humans.[2] Clearly other options are needed. According to a number of recent studies and simulations,[3–5] with the current strategies, elimination of onchocerciasis will not be feasible within the timelines of the United Nations Sustainable Development Goals,[6] i.e. 90% reduction in the number of people requiring intervention by 2030, or the previous goals set by the World Health Organization (WHO) to eliminate onchocerciasis in 80% of African countries by 2025.[7]

New treatments are needed to improve individual clinical care for patients, reduce human suffering, achieve cure and ensure advancement toward the WHO's goal of elimination by providing additional tools to shorten the timelines for elimination.

Ivermectin, the current treatment of onchocerciasis used in MDA programs, is microfilaricidal, killing only the larvae (mf). Although ivermectin is effective in reducing transmission cycles, therapy must be repeated at regular intervals (6 or 12 months) for 10-15 years, making implementation of a sustainable MDA program challenging and extremely difficult in some endemic countries. In addition, there are limitations with the use of ivermectin in zones where *Loa loa* is co-endemic. It has become clear that elimination may not be feasible by 2025 and success highly depends on local pre-control endemicity, past and future (therapeutic) coverage patterns, and geographic coverage. If MDA coverage is lower or the fraction of systematic non-adherers is higher than assumed in the simulations, the effectiveness of interventions will likely deviate from the model predictions and further delay the timeline to elimination. Recent modelling using ONCHOSIM predicts there will be around 10 million infected individuals with positive skin microfilaria in the areas covered by African Program for Onchocerciasis Control (APOC) in 2025,[8] with > 6 million manifesting clinical symptoms.[9] The total population at risk will be approximately 200 million in the countries formerly covered by APOC. Modelling activities have begun to assess the impact of a macrofilaricidal drug complementing or replacing current elimination activities. Preliminary results show that the timelines would shorten by 40-50% under both MDA and test-and-treat (TNT) strategies.

In summary, while MDA is effective in reducing transmission and morbidity in some settings, a drug that kills the adult worm or has a long-term inhibition of embryogenesis, offers the advantage of reducing the need for multiple cycles of MDA and would be an essential addition

to the global strategy to eliminate onchocerciasis. A new macrofilaricide or long-term treatment would be useful for:

- MDA, if the safety and tolerability profile and the duration of treatment are suitable, in order to drastically reduce the number of MDA cycles from 10-15 years as currently required.
- TNT strategies, for treatment of patients in endemic areas outside MDA campaigns when diagnostic tools are available, especially in "mop up" campaigns after the disease burden has been reduced by MDA programs rendering them no longer cost effective, or in areas where regular ivermectin distribution is difficult.
- Test-and-not-treat (TaNT) campaigns in areas where *Loa loa* is co-endemic, if the macrofilaricidal drug also has rapid microfilaricidal activity.
- Appropriate medical care .

2.2 Summary of Non-clinical Data

2.2.1 Summary of Non-clinical Efficacy

ABBV-4083 is a novel macrolide antibacterial that is highly potent against *Wolbachia*, the symbiotic endobacteria present in the filarial nematodes responsible for onchocerciasis. It is chemically derived from the common veterinary macrolide antibiotic tylosin and has a spectrum of activity across a panel of pathogenic bacteria similar to that of other macrolides. ABBV-4083 is uniquely potent against *Wolbachia*, with EC_{50} values of 0.022 and 0.75 nM in insect cells and cultured *Brugia malayi* microfilariae, respectively.[10] ABBV-4083 is not directly -cidal to filarial worms,[11] but only elicits its effects indirectly through depletion of *Wolbachia*.

ABBV-4083 was shown to effectively deplete *Wolbachia* in several in vivo models of filarial nematode infection. Following oral administration in mouse or jird (Mongolian gerbil) hosts implanted with either larval or adult stages of *Brugia malayi*, treatment with ABBV-4083 resulted in > 95% depletion of *Wolbachia*.[12,13] Similarly, ABBV-4083 depleted > 95% of *Wolbachia* within *Onchocerca ochengi* adult worms implanted into jirds,[14] and within *Litomosoides sigmodontis* in naturally infected jirds.[15,16] ABBV-4083 treatment also resulted in the sterilisation of *Brugia malayi* and *Litomosoides sigmodontis* female adult worms, as evidenced by a > 90% decline in microfilariae after several weeks.[13,15,16] ABBV-4083 also demonstrated additivity/synergy in association with albendazole, as evidenced by a > 99% decline in microfilariae at doses of each agent that were ineffective when dosed alone.[19] Finally, up to four non-consecutive daily treatments within a 14-dose regimen did not significantly erode *Wolbachia* depletion in *Litomosoides sigmodontis* female adult worms.[20]

ABBV-4083 has also recently been shown to be additive/synergistic with albendazole in preclinical filarial models. The addition of albendazole has been shown to be beneficial for the depletion of *Wolbachia* with doxycycline in preclinical models,[17] as well as in a recent clinical trial.[18] In contrast, albendazole itself has shown very low anti-*Wolbachia* activity in preclinical studies.

2.2.2 Summary of Safety Pharmacology Data

ABBV-4083 was tested in safety pharmacology studies including assessing effects on the CNS, cardiovascular, and respiratory systems. In a panel of off-target binding assays, ABBV-4083 displaced control-specific binding by > 50% in the NK_1 (IC_{50} 0.22 μM) and GABA-gated Cl^- channel (IC_{50} 9.1 μM) assays.[21,22] ABBV-4083 produced no neurobehavioral effects in a GLP

functional observation batter in rat through the highest dose of 300 mg/kg (maximum blood concentration [C_{max}] 1.86 µg/mL).[23,24] ABBV-4083 decreased hERG tail current in vitro by 30% at the highest concentration of 26.0 µg/mL (IC_{50} > 26.0 µg/mL).[25] In a telemetry-instrumented GLP dog study, ABBV-4083 had no effect on mean arterial pressure, heart rate or the electrocardiogram (ECG; QRS, RR, PR, and QT intervals) through the highest oral dose of 60 mg/kg (C_{max} 2.73 µg/mL).[26,27] In a GLP study, ABBV-4083 produced no effect on respiratory function through the highest dose of 300 mg/kg (C_{max} 1.86 µg/mL).[28,24]

2.2.3 Summary of Non-clinical Pharmacokinetic and Drug Metabolism Data

The ABBV-4083 pharmacokinetic profile in CD-1 mice, Sprague-Dawley rats, beagle dogs and cynomolgus monkeys was characterised by high plasma clearance, high volumes of distribution (V_{ss} > 2 L/kg) and short to moderate plasma elimination half-lives ($t_{1/2}$ 0.8 – 4.7 hr) following single intravenous doses.[29] ABBV-4083 oral bioavailability was low in mice, rats, and monkeys (3.2%, 6.5%, 2.8%, respectively), with higher values in dog (17.4%). At steady state, there were no apparent sex differences in rats or dogs. ABBV-4083 exposures on Day 28 trended higher or were comparable to Day 1 following once daily dosing in rats and dogs.[24,27]

ABBV-4083 has moderate plasma protein binding across species, with a mean unbound fraction at 1 µM of 0.071, 0.081, 0.11 and 0.076 for mice, dogs, monkeys and humans, respectively.[30]

Mean total recovery of excreted radioactivity from the bile duct cannulated rats was 90.4% after the 6 mg/kg intravenous dose or 92.5% after a 100 mg/kg oral dose.[31] Drug-related radioactivity was mainly eliminated via the biliary route (60.6% of the intravenous dose). Renal elimination was minor (8.0% of the intravenous dose). Of the radioactivity recovered in the bile, 18.4% was unchanged parent drug (19.3% of the dose). Cysteine conjugate M5 accounted for about 32% of dose recovered in the bile, urine and faeces. Other metabolites were present at low or trace levels, each less than 10% of dose. M10 (hydrate) and co-eluting metabolites M11x (hydrate)/M5 (cysteine conjugation) were the major circulating components accounting for 39.7% and 34.6% of the radioactivity in plasma, respectively; unchanged parent drug accounted for 25.6% of plasma radioactivity.[31]

In human liver microsomes, ABBV-4083 is a direct inhibitor of CYP3A4 (midazolam as a substrate) with an IC_{50} of 26 µM, with all other isoforms exhibiting IC_{50} values greater than 30 µM.[32] No time-dependent inhibition was observed at ABBV-4083 concentrations up to 50 µM. ABBV-4083 inhibited UGT1A1 in human liver microsomes, with an IC_{50} of 3.4 µM. ABBV-4083 does not increase CYP1A2, 2B6 or 3A4 mRNA expression at concentrations up to 20 µM in human hepatocyte incubations.[33] At the projected therapeutic dose, i.e. 400 mg once daily (QD), ABBV-4083 is predicted to have no perpetrator drug interaction (AUCR < 2) with CYPs using the United States Food and Drug Administration (FDA)'s mechanistic static model.[34] In vitro, ABBV-4083 is metabolised primarily by CYP3A; co-administration with CYP3A inhibitors or inducers is likely to modulate the ABBV-4083 concentrations.

In vesicles, ABBV-4083 inhibited P-gp and BCRP with IC_{50} values of 0.98 and 4.1 µM, respectively; the IC_{50} values for P-gp and BCRP in MDCK cells were markedly higher (60 and 11 µM, respectively), likely due to the low cellular permeability of the compound.[35] ABBV-4083 inhibited the uptake transporters OATP1B1 and OATP1B3 with IC_{50} values of 2.5 and 1.1 µM, respectively. IC_{50} values for OCT1, OCT2, OAT1, OAT3, MATE1, and MATE2K were estimated to be > 30 µM. Based on the transporter inhibition decision trees,[34] inhibition of P-gp, BCRP and OATP1B1/3 are expected at the 400 mg clinical dose.

ABBV-4083 is a substrate for P-gp but not for BCRP.[35]

2.2.4 Summary of Toxicology Data

The toxicity profile of ABBV-4083 has been characterised in 4-week GLP-compliant repeat dose studies in rats and dogs.[24,27] These toxicity studies have identified the dog as the most sensitive species. All haematology, coagulation, and clinical chemistry effects in the rat were considered non-adverse and wholly reversed following the 4-week recovery period, with the exception of globulin. In the dog, hepatocellular and hepatobiliary findings were seen and considered adverse only at the high dose of 60 mg; these findings were resolved or partially resolved at the end of the recovery period. Microscopic findings were associated with elevated hepatic enzyme activities (ALP, GGT, ALT, AST) and total bilirubin concentration at the end of the dosing period; the minimal bile ductule hyperplasia present at the end of the recovery period was consistent with the partial resolution of adverse biliary effects and was reflected in the corresponding temporal changes in liver-related serum chemistries. There were no effects on the liver among animals at 5 or 15 mg/kg/day at the end of the dosing period. The NOAEL in the dog was established as the mid dose, 15 mg/kg/day, and was associated with a C_{max} of 0.849 µg/mL and whole blood exposure (AUC_{0-24}) of 2.26 µg•hr/mL.

ABBV-4083 presents no genetic toxicity risk to healthy subjects in the Phase-I study. A potential for direct mutation was not detected in the in vitro bacterial reverse mutation, mouse lymphoma or the in vivo PIG-a mutation assays.[36,37,38] The in vivo rat micronucleus study (bone marrow), including an evaluation of liver, stomach, and blood for DNA strand breaks (comet assay), was negative.[39] ABBV-4083 was evaluated in GLP-compliant embryo-foetal development studies in the rat,[40] as well as the mouse[41] and is not teratogenic or fetotoxic.

In support of the Phase-II trial, a GLP-compliant 7-day toxicity study was conducted in dogs to examine the effects of ABBV-4083 when dosed in combination with albendazole.[42] The ABBV-4083 doses (5 and 15 mg/kg/day) were selected to provide exposures comparable to those obtained from a 400 mg clinical dose and a small multiple. The albendazole dose (50 mg/kg/day) targeted exposures of the albendazole sulfoxide metabolite comparable to a literature average of values obtained from a 400 mg albendazole dose. All study findings were non-adverse and reversible by the end of the 28-day recovery period. The primary microscopic effect observed was in the liver (non-adverse minimal increased cellularity of bile ductular epithelium and minimal periductular mixed cell infiltrates) at 15 mg/kg/day with or without 50 mg/kg/day albendazole. The NOAEL in this GLP study was the highest combination dose tested, 15/50 mg/kg/day.

A summary of all toxicology studies conducted with ABBV-4083 is presented in the Investigator Brochure.

2.3 Summary of Clinical Data

2.3.1 Phase-I Study in Healthy Subjects

Study M16-710 was a Phase-I first-in-human (FIH) study in 3 parts.[43] Part 1 was a randomised, double-blind, placebo-controlled single ascending dose (SAD) study. Part 2 was a randomised, single-dose, open-label, two-period cross-over food effect (FE) study. Part 3 was a randomised, double-blind, placebo-controlled multiple ascending dose (MAD) study.

In the FIH study, single (40 mg up to 1000 mg [n=48 subjects]) and multiple (100, 200 or 400 mg once daily for 7 days [n=18] and 200 or 400 mg once daily for 14 days [n=12]) doses were

administered. A total of 78 healthy subjects have been exposed to ABBV-4083 (36 in Part 1, 12 in Part 2, and 30 in Part 3) and 22 received a placebo.

In Part 1 (SAD), each of Groups 1 through 6 consisted of 6 subjects treated with ABBV-4083 40 mg, 100 mg, 200 mg, 400 mg or 1000 mg, and 2 subjects treated with placebo.

In Part 2 (FE), 12 subjects in Group 7 received ABBV-4083 1000 mg under either fasting or fed conditions.

In Part 3 (MAD), each dose group, numbered 8 through 12, consisted of 6 subjects who received ABBV4083 100, 200 or 400 mg QD × 7 days; or 200 or 400 mg QD × 14 days and 2 subjects who received placebo.

2.3.1.1 Summary of Phase-I Safety Information

In Part 1, treatment-emergent adverse events (TEAEs) were reported in 16.7% of ABBV-4083-treated subjects and 0% of placebo-treated subjects. The most common (≥ 5%) TEAEs for ABBV-4083-treated subjects were nausea (8.3%) and headache (5.6%). A single subject in the 100-mg group experienced Grade-1 elevated alanine aminotransferase (ALT) on Study Day 3, resolving on Study Day 14.

In Part 2, TEAEs were reported in 58.3% of ABBV-4083-treated subjects (66.7% in fasting subjects and 50.0% in fed subjects). The most common (≥ 10%) TEAEs for ABBV-4083-treated subjects were nausea (25.0%), diarrhoea (16.7%), headache (16.7%), hepatic enzyme increased (16.7%) and vomiting (16.7%). During the fasting period, 2 subjects experienced asymptomatic and reversible elevated ALT and/or aspartate aminotransferase (AST) values at Grade 1. In the fed period, 2 subjects experienced mild adverse events (AEs) of elevated serum liver enzymes leading to discontinuation of study drug: one subject experienced asymptomatic and reversible Grade-2 elevated ALT and/or AST 6 days after receiving a single 1000 mg dose of ABBV-4083, and 1 subject experienced asymptomatic and reversible Grade-4 elevated ALT and/or AST 3 days after receiving a single 1000 mg dose of ABBV-4083. No accompanying total, direct, or indirect bilirubin elevations were observed. The Investigator considered the AEs to have a reasonable possibility of being related to ABBV-4083. The effect of food on exposure parameters, i.e. C_{max} or area under the blood concentration-time curve (AUC), was minimal.

Independent internal and external drug-induced liver injury experts were consulted. In accordance with their advice, the single dose of 400 mg was tested again in Part 1 Group 6 (n = 6 subjects) with extended monitoring from 3 to 10 days. No above normal transaminase levels were observed. This was followed by the MAD portions of the study (Part 3) with the same extended monitoring period.

In Part 3, three subjects experienced Grade-1 elevated ALT and/or AST in the dose group receiving 100 mg QD × 7 days. No elevated transaminase levels were observed in the dose groups receiving 200 or 400 mg × 7 days or 200 or 400mg QD × 14 days. All transaminase elevations were asymptomatic and reversible, and none were accompanied by elevated bilirubin levels. TEAEs were reported in 33.3% of ABBV-4083-treated subjects and 30.0% of placebo-treated subjects. The most common (≥ 5%) TEAEs for ABBV-4083-treated subjects were headache (6.7%), nausea (6.7%), palpitations (6.7%) and medical device site reaction (6.7%).

In this FIH study, one serious adverse event (SAE), which was of fatal outcome, was reported and was assessed as not related to ABBV-4083: the subject, who received a single 1000 mg dose of ABBV-4083 on Day 1 under fed conditions in Period 1 of Part 2, experienced an SAE of unconfirmed pulmonary embolus, which resulted in death on Day 9 post-dosing. The

Investigator considered the death to be not related to the study, and more likely related to the subject's hypercoagulable state at baseline, i.e. underlying risk factor for thrombocytosis and hypercholesterolemia.

2.3.1.2 Summary of Phase-I Pharmacokinetic Information

All 78 subjects, i.e. 36 subjects from Part 1, 12 subjects from Part 2, and 30 subjects from Part 3, who received ABBV-4083 were included in the pharmacokinetic analyses.

Pharmacokinetic (PK) results from Parts 1 and 3 of Study M16-710 suggested that maximum concentrations of ABBV-4083 were achieved around 1.5 to 2 hours with a half-life less than 4 hours at doses ≤ 400 mg. C_{max} and AUC increased in a slightly more than dose-proportional and predictable manner. Following multiple dose administration, the concentrations on Day 1 and Day 14 appeared to be similar. There did not appear to be a relationship between ABBV-4083 concentrations and QTcF from baseline, suggesting that ABBV-4083 has no clinically relevant effects on QTc prolongation. The effect of food on exposure parameters, i.e. C_{max} and AUC, was minimal.

2.3.2 Conclusion on Clinical Data to Date

In summary, no safety concerns have been identified to date for ABBV-4083 in doses up to 400 mg/day QD for 14 days based on the FIH study. There was only one serious adverse event (SAE), of fatal outcome and assessed as not-related to ABBV-4083, reported after administration of a single dose of 1000 mg, in the FIH study. Elevated liver enzymes were seen after a 1000 mg single dose of ABBV-4083, but no hepatotoxicity was seen with multiple doses of ABBV-4083 up to 400 mg QD for 14 days.

Taking into consideration the non-clinical data (see Section 2.2) and first data in human (see Section 2.3.1), one potential safety effect is currently under consideration: "alterations in liver tests". Therefore, monitoring of biochemistry laboratory tests, including liver tests, is required to further assess this potential safety effect during the upcoming clinical trials.

The results from the Phase-I study in healthy male and female subjects support continuation of the clinical development programme of ABBV-4083 as treatment for onchocerciasis.

Further details can be found in the Investigator Brochure, which contains comprehensive information on ABBV-4083.

2.4 Design and Rationale for Study

2.4.1 Overview of Study Design

This phase-II study in subjects with onchocerciasis will be an adaptive study with two parts. In Part 1 (proof-of-concept [PoC]), four regimens of ABBV-4083 ± albendazole will be assessed in comparison to albendazole alone with the aim of selecting two regimens having optimal activity and safety to continue into Part 2 Regimen Selection. Part 1 will end at 6 months follow-up, and the study will be paused to evaluate nodules to determine whether the ABBV-4083 + albendazole combinations are superior to both ABBV-4083 and albendazole alone, and to select the optimal arms to continue into Part 2 (see Figure 1, Figure 2 and Figure 3). Based on earlier studies, albendazole alone is not expected to affect *Wolbachia* levels[18] or to substantially interfere with embryogenesis in female worms.[44] The albendazole arm is therefore considered largely equivalent to an untreated control arm for efficacy. Selection of the regimens

for Part 2 will take into consideration the balance of efficacy, i.e. analysis of *Wolbachia* depletion in adult worms as surrogate marker, supported by effects on embryogenesis in female worms, as well as safety and convenience, i.e. the number and duration of drugs taken. The target efficacy for Part 1 will be based on comparison to studies using doxycycline, which produces ≥ 90% *Wolbachia* depletion at 6 months.[18,45] This level of *Wolbachia* depletion at Month 6 has been correlated with the absence of skin mf at longer-term time-points.[45]

Part 2 is a 24-month study designed to select the optimal regimen for progression to Phase III. The primary endpoint is the absence of skin mf at Month 24, which is the accepted endpoint for registration and was confirmed by US FDA. Positive results in Part 1 of the study (PoC), based on all safety, tolerability and efficacy available data, will initiate continuation of the study into Part 2 (Regimen Selection). Up to two regimens will be chosen from Part 1 and additional subjects will be enrolled. Provided that the combination rule has been satisfied based on data on *Wolbachia* depletion in Part 1, i.e. that ABBV-4083 + albendazole is superior to either agent alone of equal duration, the active arms in Part 2 will be compared to placebo. If the combination rule has not been satisfied in Part 1, the comparator arm will be ABBV-4083 400 mg QD for 7 days, (based on the assumption that the superiority of a combination arm to albendazole alone (Arm E) will have been achieved), and the combined Month 6 data from Parts 1 and 2 will be used to satisfy the combination rule.

2.4.2 Rationale for the Study

Adult filarial worms causing onchocerciasis carry an obligate symbiotic endobacterium, *Wolbachia*, which is essential for development, fecundity, and ultimate survival.[46,47] Clinical studies with the antibiotic doxycycline, which depletes endobacterium populations but has no direct effect on the host worms, have demonstrated the death of adult worms over time after antibacterial therapy.[18,48–51] This indirect, anti-*Wolbachia* approach to the treatment of onchocerciasis brings several advantages that are considered particularly desirable for a new antifilarial agent, for the following reasons.

- It may avoid the side effects caused by the rapid death of microfilariae. Treatment with ivermectin is rapidly microfilaricidal and can produce a systemic inflammatory reaction associated with the release of both microfilarial and *Wolbachia* antigens from dying microfilariae, called Mazzotti reaction. Treatment with an anti-*Wolbachia* agent only interrupts the production of microfilariae, resulting in a slow decline in microfilarial levels. Adult worm death also occurs, but very slowly i.e. ≥ 2 years after treatment, avoiding the potential for inflammation due to rapid death of the adult worms.[49]
- It produces long-term sterilisation of adult female worms. In contrast to treatment with ivermectin, which primarily affects the late stages of microfilarial development and produces only temporary worm sterilisation, treatment with an anti-*Wolbachia* agent has been shown to interfere with embryogenesis for at least 24 months.[49,50]
- It has the potential to interrupt transmission shortly after treatment, even before microfilarial levels decline. Rapid depletion of *Wolbachia* within microfilariae has been shown to retard the development of larvae within the insect vector following ingestion.[54]
- It has the potential to modulate disease pathology. While live *O. volvulus* microfilariae are relatively benign, the release of *Wolbachia* endotoxin-like products from degenerating microfilariae creates a proinflammatory stimulus that has been shown to produce keratitis (corneal inflammation) in a mouse model.[55] Depletion of *Wolbachia* by antibacterial therapy may thus reduce ocular and possibly also skin pathology.

- It is expected to be especially beneficial in regions co-endemic with *Loa loa*, where anti-microfilarial treatment is challenging, due to potential severe AEs related to the rapid death of *Loa loa* microfilariae in the blood. *Loa loa* worms do not carry the *Wolbachia* endosymbiont and a microfilaricidal effect on *Loa loa* is not expected.[51]
- Finally, it has also been shown to be effective in lowering microfilariae in regions with suboptimal response to ivermectin.[48]

Although doxycycline is effective as a macrofilaricide via its anti-*Wolbachia* activity, it is contraindicated in pregnant women and children through the age of 8 years due to developmental toxicities. Furthermore, 4 to 6 weeks of daily therapy with doxycycline is required to lower the *Wolbachia* population sufficiently to produce a -cidal effect in the adult worm. Consequently, doxycycline is unsuitable for MDA and far from ideal for subject management. Therefore, agents with better safety profiles and more rapid onset of action are needed. The *Wolbachia* endobacterium is not susceptible to many traditional classes of antibacterials and screening for novel anti-*Wolbachia* agents was conducted with support from the Bill & Melinda Gates Foundation and the Global Health Innovative Technology Fund.[56]

In conjunction with the Anti-*Wolbachia* Consortium (AWOL) based at the Liverpool School of Tropical Medicine, screening of a collection of antibacterials supplied by AbbVie led to the identification of tylosin A (TylA), a known veterinary antibacterial, as a promising lead. Preliminary studies with TylA suggested that it could effectively clear the *Wolbachia* bacterium in a mouse model of filariasis when delivered intraperitoneally to a greater extent than doxycycline and at shorter dosing regimens. However, the PK profile of TylA appears to be permeability limited, and oral administration produced only a marginal effect. This was corroborated by PK studies in mice suggesting that the oral bioavailability of TylA is ≤ 1%.

Analogues of TylA with improved permeability were subsequently identified, leading to markedly enhanced drug exposure upon oral dosing. A subset of these PK-improved analogues, including ABBV-4083, also demonstrated superior anti-*Wolbachia* potency *in vitro*. This combination of properties greatly improves its ability to deplete the endosymbiont as an orally delivered drug.

ABBV-4083 is a promising candidate to kill and/or provide long-term sterilisation of the sexually mature adult *O. volvulus*. ABBV-4083 could be considered as an alternative to doxycycline if a clear advantage with a shorter regimen duration, i.e. ≤ 14 days, and a better safety profile is demonstrated. ABBV-4083 has also recently been shown to be additive/ synergistic with albendazole in preclinical filarial models, similar to results with doxycycline plus albendazole in preclinical models,[51] as well as in a recent clinical trial.[18] In contrast, albendazole alone has shown very low anti-*Wolbachia* activity in preclinical studies. The study will therefore investigate the efficacy of ABBV-4083 both alone and in combination with albendazole for 7 or 14 days.

2.4.3 Rationale for Dose Selection

ABBV-4083, albendazole, and ivermectin or matching placebo will be administered orally.

The 400 mg QD dose of ABBV-4083 administered for 7 or 14 days was tested in the FIH study (Study M16-710) and was considered safe and well tolerated. This dose maintains mean free plasma concentrations of ABBV-4083 in excess of the estimated in vitro EC_{90} for a similar period of time as a dose in jirds (50 mg/kg) that is effective following 7 or 14 days of dosing in *Litomosoides sigmodontis* infected jirds. This dose also produces a similar mean free C_{max} and longer time in excess of the in vitro EC_{90} compared to a dose in jirds (20 mg/kg) that is effective

following 7 days of dosing in combination with albendazole in *Litomosoides sigmodontis* infected jirds.

The oral dose of albendazole over-encapsulated tablets to be administered to subjects in Arms C, D and E is 400 mg QD for 7 days, 3 days and 7 days, respectively. Albendazole is given at 400 mg QD for 1 to 3 days for intestinal worms and skin nematodes such as cutaneous *larva migrans,* and at 400 mg BID for 1 to 3 days for liver flukes.[57]

Higher daily doses (400 mg BID) for prolonged periods up to 84 days total are indicated for more disseminated systemic infections such as echinococcosis and neurocysticercosis.[58] Since mild to moderate elevations of liver enzymes have been reported with the higher/more prolonged dose,[58] and the 400 mg QD dose produces plasma exposure of the active metabolite (albendazole sulfoxide) roughly equivalent to the exposure shown to be active in combination with ABBV-4083 in preclinical efficacy studies, this dose was selected for combination with ABBV-4083. In the preclinical *Litomosoides sigmodontis* model in jirds, as few as 3 days of albendazole combined with 7 days of ABBV-4083 produced strong signals of *Wolbachia* depletion and female adult worm sterilisation,[59] providing the basis for the duration of dosing in Arm D. Plasma concentrations of albendazole sulfoxide are increased by administration with food,[60,61] therefore albendazole will be administered with food in this study.

Ivermectin over-encapsulated tablets will be given at the standard MDA dose as a single oral dose of 150 µg/kg body weight at Month 6 in Part 2 of the study to subjects who receive ABBV-4083 matching placebo plus albendazole matching placebo.[65,68] Some subjects receiving ABBV-4083 ± albendazole regimens in Part 2 will also receive over-encapsulated ivermectin at Month 6 while the remainder of subjects will receive ivermectin matching placebo, in order to assess the effect of a dose of ivermectin at Month 6 on efficacy at Month 24. No subjects receiving active ABBV-4083 ± albendazole in Part 2 are deemed at significant risk of ocular or other clinical progression without a dose of ivermectin at Month 6, since regimens will only be advanced into Part 2 on the basis of a strong signal of *Wolbachia* depletion in Part 1. Active anti-*Wolbachia* treatment is expected to produce a slow decline in skin microfilariae over time due to the sterilisation of adult female worms, lowering the likelihood of the appearance of ocular microfilariae. In addition, studies have shown that ocular disease progression is slow and is highly associated with microfilarial invasion into the eyes. Frequent ophthalmological examinations will be conducted, and unblinded ivermectin will be provided as rescue therapy at the discretion of the Investigator. Therefore, the study plan provides adequate measures to ensure the safety of all subjects in Part 2 who do not receive ivermectin at Month 6.

3 Study Design

3.1 Overall Study Design

DNDi-TYL-01 will be a multicentre, randomised, active and/or placebo-controlled, double-blind, parallel-group, adaptive Phase-II study in two parts. It will be conducted in at least two investigational centres, with competitive recruitment. Additional centres may be included. All centres must however have access to appropriate medical facilities to treat severe AEs.

Part 1 will use a surrogate endpoint of *Wolbachia* depletion in adult female worms to:

- establish proof of concept for ABBV-4083 in onchocerciasis by demonstrating superiority of the regimens of ABBV-4083 alone over the control regimen, albendazole alone, which has been shown to have little or no activity in onchocerciasis,[62,44]

- establish the activity of ABBV-4083 and albendazole in combination by demonstrating superiority of a regimen of ABBV-4083 + albendazole over regimens of ABBV-4083 and albendazole alone of equal duration, and
- establish up to two preferred regimens of ABBV-4083 and/or ABBV-4083 + albendazole to progress into Part 2 of the study.

Each subject's participation in Part 1 of the trial will last approximately 6½ months, excluding the screening period, which may be up to 8 weeks. At Month 6, Part 1 will end, and the study will be paused to evaluate the nodules and skin mf. Part 1 data will be unblinded to the Sponsor and analysed to allow for finalisation of the study design in Part 2. Enrolment will then resume in Part 2.

Part 2 will use a clinically relevant endpoint of depletion of skin microfilariae at Month 24 to:

- identify the preferred regimen of ABBV-4083 or ABBV-4083 + albendazole to progress into Phase-III studies, and
- evaluate the effect of a dose of ivermectin 6 months after ABBV-4083 or ABBV-4083 + albendazole on skin microfilarial density at Months 12, 18 and 24.

If the superiority of ABBV-4083 + albendazole over ABBV-4083 alone is not demonstrated in Part 1, surrogate endpoint data from Part 2 (i.e. *Wolbachia* depletion in adult worms at Month 6) from Arms with ABBV-4083 + albendazole and ABBV-4083 alone will be combined with data from Part 1 to assess the superiority of ABBV-4083 + albendazole to ABBV-4083 alone (Part 2 Alternate Scenario).

Each subject's participation in Part 2 of the trial will last approximately 24½ months, excluding the screening period, which may be up to 8 weeks. The set of subjects in Part 2 is fully independent from the set of subjects in Part 1. The final analysis will be conducted at the end of Part 2.

A Safety Review Committee (SRC) and an independent Data and Safety Monitoring Board (DSMB) will be appointed (See Sections 13.2 and 13.3).

3.2 Study Design - Part 1

In Part 1, a total of 150 subjects will be recruited, and will be randomised continuously 1:1:1:1:1 into one of five parallel treatment arms until group size is achieved. Within each treatment arm, participants will be stratified by the number of operable sites with onchocercomata. There will be two strata, i.e. one site and more than one site.

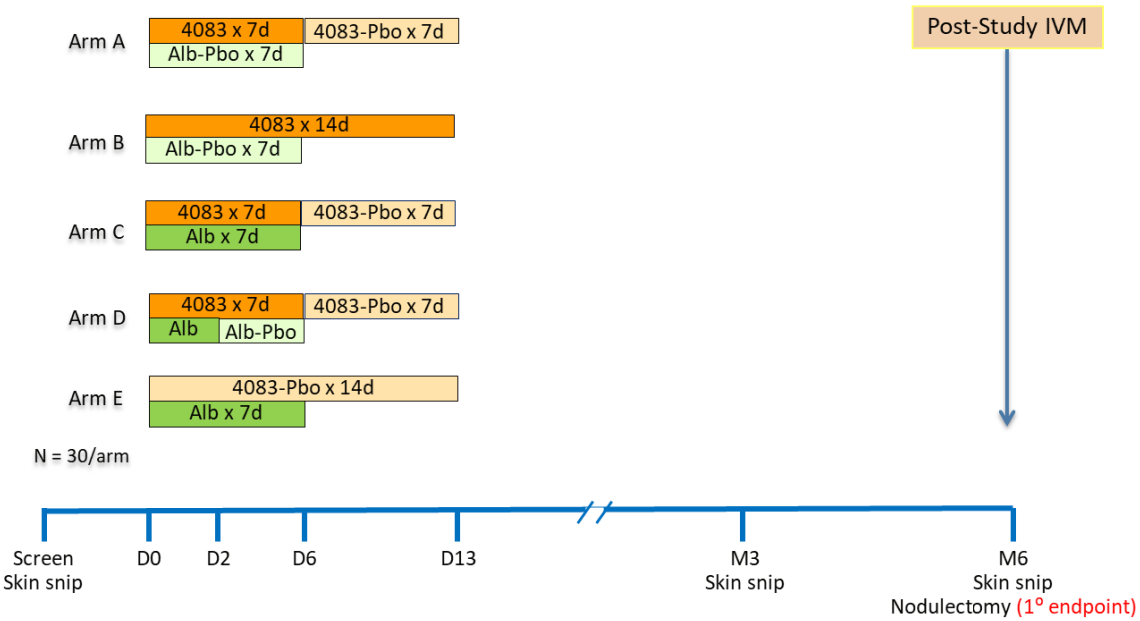
The five treatment arms are defined as follows:

- Arm A (N = 30): 7 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 matching placebo
- Arm B (N = 30): 7 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 400 mg
- Arm C (N = 30): 7 days of ABBV-4083 400 mg + albendazole 400 mg followed by 7 days of ABBV-4083 matching placebo
- Arm D (N = 30): 3 days of ABBV-4083 400 mg + albendazole 400 mg followed by 4 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 matching placebo
- Arm E (N = 30): 7 days of ABBV-4083 matching placebo + albendazole 400 mg followed by 7 days of ABBV-4083 matching placebo

Details of timing and sequence of investigations and measures are provided in the Schedule of Events (see Appendix 1). The overall design for Part 1 is presented in Figure 1.

Post-study ivermectin will be given to all participants after nodulectomy at 6 months.

Figure 1. Overall Design for Part 1



4083 = ABBV-4083; Alb = albendazole; d = days; D = (study) day; IVM = ivermectin; M = month; Pbo = placebo

3.3 Study Design - Part 2

For Part 2, up to two treatment arms from Part 1 that are likely to demonstrate high efficacy at Month 24 (based on Part 1 efficacy data and historical studies with doxycycline) and safety will be selected as treatment arms in Part 2. The choice will take into consideration feasibility to use the regimen as potential future treatment.

In order also to assess the effect of a dose of ivermectin at Month 6, participants will be randomised into four treatment arms, with the best candidate based on Part 1 results administered with ivermectin and with ivermectin placebo at Month 6.

Within each treatment arm, subjects will be stratified by the number of operable sites with onchocercomata and by mean screening skin mf. There will be four strata, i.e. 1 site and less than or equal to 5 mf/mg, more than 1 site and less than or equal to 5 mf/mg, 1 site and more than 5 mf/mg, more than 1 site and more than 5 mf/mg.

A total of either 294 subjects (Base Scenario) or 336 subjects (Alternative Scenario) will be recruited. The Base Scenario will be employed:

- if neither Arm C nor Arm D from Part 1 is selected for continued enrolment in Part 2, or
- if either Arm C and/or Arm D in Part 1 is selected for continued enrolment in Part 2 and Arm C and/or Arm D has demonstrated superiority over both Arm E and Arm A in Part 1.

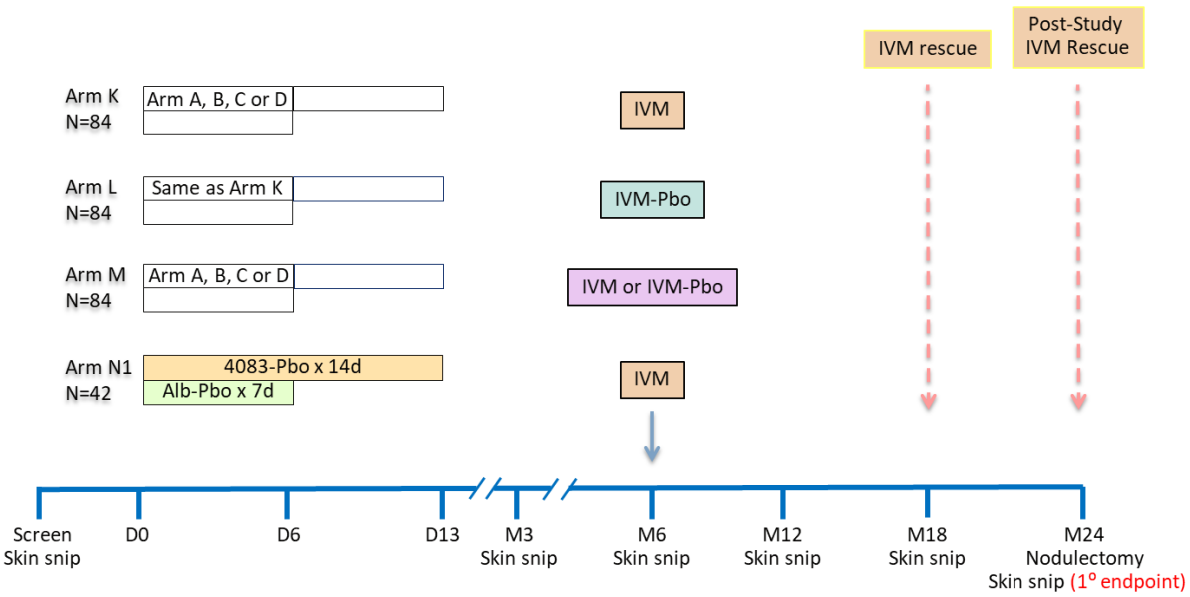
The Alternative Scenario will be employed if either Arm C and/or Arm D in Part 1 is selected for continued enrolment in Part 2, but Arm C or Arm D in Part 1 has not demonstrated statistical superiority over both Arm E and Arm A.

In the Base Scenario, subjects will be randomised continuously 2:2:2:1 into one of four parallel treatment arms until group size is achieved:

- Arm K (n = 84): initial treatment with an active regimen selected from Part 1, followed by ivermectin at Month 6;
- Arm L (n = 84): initial treatment with the same active regimen selected from Part 1 as Arm K, followed by ivermectin matching placebo at Month 6;
- Arm M (n = 84): initial treatment with a second active regimen selected from Part 1, followed by either ivermectin or ivermectin matching placebo at Month 6 (decision to be made prior to Part 2);
- Arm N1 (n = 42): initial treatment with ABBV-4083 matching placebo and albendazole matching placebo, followed by ivermectin at Month 6.

Details of timing and sequence of investigations and measures are provided in the Schedule of Events (see Appendix 2). The overall design for Part 2 Base Scenario is presented in Figure 2.

Figure 2. Overall Design for Part 2 - Base Scenario



4083 = ABBV-4083; Alb = albendazole; d = days; D = (study) day; IVM = ivermectin; M = month; Pbo = placebo

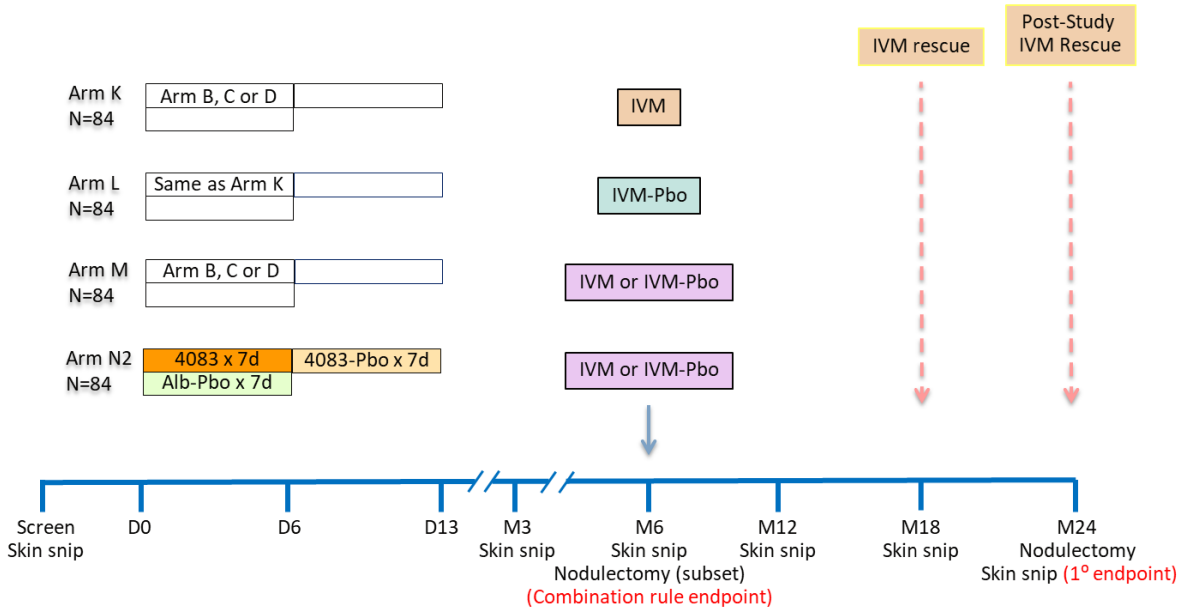
In the Alternate Scenario, subjects will be randomised continuously 1:1:1:1 into one of four parallel treatment arms until group size is achieved:

- Arm K (n = 84): initial treatment with an active regimen selected from Part 1, followed by ivermectin at Month 6;
- Arm L (n = 84): initial treatment with the same active regimen selected from Part 1 as Arm K, followed by ivermectin matching placebo at Month 6;
- Arm M (n = 84): initial treatment with a second active regimen selected from Part 1, followed by either ivermectin or ivermectin matching placebo at Month 6 (decision to be made prior to Part 2);

- Arm N2 (n = 84): 7 days of ABBV-4083 400 mg plus appropriate duration of albendazole matching placebo and ABBV-4083 matching placebo followed by either ivermectin or ivermectin matching placebo at Month 6 (decision to be made prior to Part 2).

In the Alternate Scenario, a minimum of 84 subjects with two or more operable sites will be enrolled to allow for approximately 21 subjects per arm to undergo a single-site nodulectomy at Month 6 for the evaluation of *Wolbachia* depletion but still have remaining onchocercomata for evaluation of skin microfilariae and other endpoints at Month 24. The overall design for Part 2 Alternative Scenario is presented in Figure 3.

Figure 3. Overall Design for Part 2 - Alternative Scenario



4083 = ABBV-4083; Alb = albendazole; d = days; D = (study) day; IVM = ivermectin; M = month; Pbo = placebo

Rescue treatment with ivermectin will be offered at the investigator discretion to subjects with clinically significant worsening of symptoms and / or signs related to onchocerciasis at any time during the study or to subjects with increased mean number of microfilariae in the skin at Month 18, compared to the mean number at Month 12.

Post-study ivermectin will be provided after nodulectomy at 24 months to any subject with positive skin and/or eye microfilariae.

3.4 End of Study

The end of study for an individual subject is his or her "last visit" defined as the latest of the following:

- screening failure, or
- the End of Study visit (see Schedules of Events in Appendix 1 and Appendix 2), or
- early termination visit, or
- for subjects lost to follow-up or withdrawn, the last visit the subject attended.

The overall end of the study is defined as the last visit, as defined above, of the last subject.

If a decision is taken to terminate the study early, the study will end when the Sponsor notifies the Investigator, the regulatory authorities and ethics committee(s) in writing that the study has been stopped, or when the "last visit" as defined above occurs for the last subject, whichever is later.

3.5 Assessment and Management of Risks

3.5.1 Risks associated with the IMPs

This section provides information on the main risks identified for the subjects who will take part in the trial, based on protocol design. This list is not exhaustive. Refer also to the ABBV-4083 Investigator Brochure and albendazole or ivermectin reference safety information.[57,58,63–65,68]

3.5.1.1 Potential and Identified Risks of ABBV-4083

At this stage of development, there is no risk management plan for ABBV-4083. In the Phase-I study, elevated liver enzymes were seen after single doses of 1000 mg ABBV-4083, but no liver toxicity was seen with multiple doses of ABBV-4083 up to 400 mg QD for 14 days. In addition, no clinically significant haematological laboratory abnormalities associated with AEs or discontinuation from the study were observed (see also Section 2.3.1.1 and Summary of data and guidance to the investigator in the Investigator Brochure). Based on data from preclinical and Phase I studies, a potential risk associated with ABBV-4083 administration is under consideration: "alteration in liver tests". Therefore, monitoring of biochemistry laboratory tests, including liver tests, is required to further assess this potential safety effect during this Phase-II study.

In vitro, ABBV-4083 is metabolised primarily by CYP3A and by cysteine conjugation; co-dosing with CYP3A inhibitors or inducers may affect ABBV-4083 concentrations. At the 400 mg dose, ABBV-4083 may inhibit P-gp and BCRP.

3.5.1.2 Potential and Identified Risks of Albendazole

Treatment with albendazole has been associated with mild to moderate elevations on hepatic enzymes that usually normalize upon discontinuation of therapy. Cases of acute liver failure of uncertain causality and hepatitis have also been reported. Subjects with abnormal transaminases before starting albendazole therapy should be carefully monitored during treatment. Liver tests should be obtained before the start of therapy and on regular basis for long duration treatment courses.

Treatment with albendazole has been shown to occasionally cause myelosuppression and therefore blood counts should be performed at the start of therapy and regularly for long duration treatment courses. Subjects with liver disease appear to be more susceptible to myelosuppression and warrant closer monitoring.

Treatment with albendazole for neurocysticercosis may cause symptoms associated with an inflammatory reaction following the death of the parasite (e.g. seizures, increased intracranial pressure and focal signs). Pre-existing neurocysticercosis may be also uncovered in patients treated with albendazole for other conditions, especially in areas with high taeniasis infection.

Treatment with albendazole has been shown to be teratogenic and embryotoxic in animal studies. Therefore, women of childbearing age should initiate treatment only after a negative

pregnancy test and should be advised to use highly effective method of contraception up to 1 month after last intake of albendazole. See in addition the albendazole package inserts for further information.[57,64]

3.5.1.3 Potential and Identified Risks of the Combination of ABBV-4083 and Albendazole

Results of a GLP-compliant 7-day toxicity study conducted in dogs to examine the effects of ABBV-4083 when dosed in combination with albendazole at exposures comparable to those expected in this clinical trial, no additive effects were seen with the combination. All study findings were non-adverse and reversible by the end of the 28-day recovery period (see Section 2.2.4). However, due to potential risk of alteration of liver tests both with ABBV-4083 or albendazole, the proposed safety monitoring in the study includes transaminases and total bilirubin levels at treatment initiation and frequent monitoring during treatment. Furthermore, the proposed adaptive design of the study, allowing for arms with lower doses of ABBV-4083 if toxicity is observed in initial arms, will mitigate the potential risk of effects on the liver with co-administration of ABBV-4083 + albendazole (see Section 3.5.2.2).

3.5.1.4 Potential and Identified Risks of Ivermectin

Treatment with microfilaricidal drugs such as ivermectin can produce a systemic inflammatory reaction associated with release of both microfilarial and *Wolbachia* antigens from dying mf. The so-called Mazzotti reaction is characterised by fever, ocular symptoms, arthralgia, synovitis, oedema, urticarial rash, pruritus, lymphadenitis, headache, myalgia, lymphadenopathy, weakness, tachycardia, nausea, conjunctivitis, diarrhoea and vomiting.[52,53] When ivermectin is administered in this study, a Mazzotti reaction may occur. Transient symptoms are likely to occur within 3 days of treatment and are usually mild requiring no more than simple reassurance. In addition, the following possible side effects have been reported with the use of ivermectin:[63,65] allergic reaction, difficulty breathing, acute hepatitis, elevated liver enzymes, elevated blood bilirubin, elevated haemoglobin or elevated eosinophil levels or presence of blood in the urine. When used for treatment of onchocerciasis, worsening of asthma have also been identified. Rarely, transient postural hypotension occurs within 12-24 hours, which responds to rest and oral administration of fluids.[68] These symptoms can be managed by the study personnel.

Mazzotti reactions are not expected with ABBV-4083: treatment with an anti-**w**olbachial agent only interrupts the production of mf, resulting in a slow decline in mf levels. Adult worm death also occurs very slowly (≥ 2 years after treatment), avoiding the potential for inflammation from rapid death of the adult worms.[50]

After administration of repeated doses of ivermectin close to or equal to maternotoxic doses, foetal abnormalities were observed in several animal species. Based on these studies, it is difficult to assess the risk of a single low dose. In clinical studies, no malformations or fetotoxic effects have been attributed to ivermectin. However, follow-up data of exposure to ivermectin during pregnancies is not sufficient to rule out any risk.[69] Therefore, as a precaution, ivermectin should not be given to pregnant women. Ivermectin is excreted in human milk at low concentrations. Treatment of breastfeeding women should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk for the newborn.[65]

3.5.2 Adverse Event and Toxicity Management

3.5.2.1 General Management

The following measures will be implemented to minimise the risks:

- Subjects with certain abnormalities on physical or neurological examination or laboratory tests that could interfere with the objectives of the trial or the safety of the subject, in the opinion of the Investigator will be excluded (see Section 6.2), as well as subjects with certain ophthalmological history or conditions;
- Physical examinations, neurological examinations and ophthalmological examinations will be conducted regularly throughout the In-house Periods, and at follow-up visits;
- Blood counts and liver tests including transaminase and bilirubin levels will be monitored regularly during treatment.
- Medications or herbal preparations are prohibited within 14 days prior to IMP intake (see Sections 6.2) and for 24 hours post last intake of the IMP (see Section 8.1) with certain specific exceptions.

3.5.2.2 Toxicity Management and Dose Adjustment

Once at least 15 subjects have been treated in each of the five arms in Part 1, the SRC will review safety results separately for each arm in a blinded way every 2 weeks and evaluate causality. The study unblinded statistician will inform the SRC before their review if > 10% of the subjects in any arm meet any of the toxicity criteria listed below, without disclosing the arm(s). In case this criterion is met, the SRC will refer to the DSMB. The DSMB may recommend halting enrolment into arms of the same or longer duration with or without albendazole added and continuing enrolment in those arm(s) of the shorter duration, as shown in Table 1. The enrolment of the closed arms may be reopened using a lower dose of ABBV-4083 at 300 mg QD with the same duration and same combination (with or without albendazole) as the original arm, in which case enrolment will continue until 30 subjects have been enrolled at that dose. However, subjects who have already started to receive 400 mg QD ABBV-4083 in the halted arm and who have not experienced dose-limiting toxicity will remain on that dose until treatment completion.

When albendazole is used in mass drug administration programs, adverse events are commonly encountered in areas where gastrointestinal helminth infection occurs.[70] It is usually well tolerated and the liver injury reported with its use has been mild and self-limited in course.[62,66,67,44] The proposed safety monitoring in the study includes blood counts and liver tests including transaminases and total bilirubin levels at treatment initiation and frequent monitoring during treatment. Furthermore, the proposed adaptive design of the study, allowing for arms with lower doses of ABBV-4083 if toxicity is observed in initial arms, will mitigate the potential risk of effects on the liver with co-administration of ABBV-4083 + albendazole.

The end of exposure is defined as one day after the last dose of IMP, which is at least five half-lives ($t_{1/2}$) after the last intake of IMP, i.e. ABBV-4083 or albendazole. The half-life of ABBV-4083 is less than 4 hours and the half-life of albendazole sulfoxide is 8-12 hours but active albendazole is administered up to Day 6 at the longest duration.

A subject will be considered to have a toxicity if they have:

- an IMP-related treatment-emergent AE leading to discontinuation, i.e. considered as having a reasonable possibility of being related to any of the IMPs, and with onset between Day 0 and 30 days after the end of treatment;
- a severe or serious IMP-related treatment emergent AE, i.e. considered as having a reasonable possibility of being related to any of the IMPs, and with onset between Day 0 and 30 days after the end of treatment;
- a Grade 3 or 4 ALT elevation during treatment, defined as between Day 0 and 2 days after the end of treatment; ALT elevations will not additionally be counted as AEs described in the previous two criteria, although they may be reported as AEs.

The SRC and DSMB will continue to monitor the toxicity criteria in Part 2, and the safety results will be cumulative from Part 1 to Part 2. That is, subjects with an event meeting the toxicity criteria during Part 1 will still count in Part 2 for the same treatment, as if the study was not paused between Part 1 and Part 2. If > 10% of subjects in any regimen meet the toxicity criteria across Parts 1 and 2, the regimen will halt but dose adjustment will not occur in Part 2. Safety will be reviewed by the SRC and DSMB using the same criteria for any arms in Part 1 that are restarted using the 300 mg ABBV-4083 dose.

3.5.2.3 Dose-adjusted Arms in the Event of Toxicity

If > 10% of subjects in an arm of Part 1 meet any of the toxicity criteria, the actions shown in Table 1 may be implemented. Decisions for dose reduction will be taken based on all available safety data including the events that trigger the dose adjustment process.

Table 1. Dose Adjustment Recommendations for Toxicity Management in Part 1

Toxicity criteria reached in	Recommended action	Rationale
Arm A or Week 1 of Arm B	Halt all study arms, then begin to enrol new Arm F, Arm G, Arm H and/or Arm I with a reduced dose of ABBV-4083 300 mg QD (n=30/arm), continue to enrol the remainder of Arm E in Arm J (to a total n=30).	Presumes that dose of ABBV-4083 is too high and that albendazole does not add to the observed toxicity.
Week 2 of Arm B	Halt Arm B, then begin to enrol new Arm G with ABBV-4083 300 mg QD (n=30)	Presumes that dosing ABBV-4083 400 mg QD is safe for 7 days but not 14 days.
Arm C	Halt Arm C, then begin to enrol new Arm H with ABBV-4083 300 mg QD (n=30)	Presumes that dosing ABBV-4083 + albendazole 400/400 mg QD is safe for 3 days but not 7 days.
Arm D	Halt Arms C and D, then begin to enrol new Arms H and I with ABBV-4083 300 mg (n=30/arm)	Presumes that dosing ABBV-4083 + albendazole 400/400 mg QD is not safe.

3.5.3 Risks Associated with Disease Progression

The clinical symptoms of onchocerciasis result from inflammatory responses to the presence of mf, ranging from itching of the skin to visual impairment and blindness due to mf in the eyes. Chronic skin and ocular symptoms develop over many years. Ocular disease in onchocerciasis is characterised by changes in both the anterior and posterior segments of the eye. Early stages typically begin with the appearance of anterior punctate lesions consisting of opacities of the

superficial corneal stroma. Long-standing and high-intensity infections, as measured by high levels of skin and ocular mf, can result in massive invasion of the cornea and other anterior regions, leading to later-stage disease including sclerosing keratitis, a progressive irreversible scarring of the cornea. [71,72] Sclerosing keratitis usually follows several years of high-intensity infection, and blindness due to this and accompanying conditions in the anterior segment, e.g. anterior uveitis, iris atrophy, anterior and posterior synechiae, secondary cataract and glaucoma, usually develop after the second decade.[72]

Subjects with mf in the posterior segment with certain ophthalmological history or conditions predisposing them to greater risk of ocular pathology progression, will be excluded from the study, as well as those with current hyperreactive onchodermatitis. Moreover, subjects with severe manifestations of onchocerciasis will be excluded from the study.

In order to avoid progression of ocular disease during the study, ivermectin may be used as rescue medication at any time at the discretion of the Investigator. Ophthalmological examinations will be performed at the visits at Month 3, 6, 12, 18 and 24, providing frequent opportunities to detect any ocular disease and introduce rescue medication (see Section 2.4.3). In addition, any subject with increasing microfiladermia at Month 18 compared to Month 12 will be administered ivermectin.

To minimize the risk of progression of onchocerciasis, ivermectin will be administered:

- at any time, at the Investigator's discretion if clinical symptoms and/or signs worsen. The most important goal of therapy is the continuous reduction of disease burden, i.e. mf levels (rescue medication).
- to all subjects when they reach the end of Part 1 at Month 6 (post-study IVM).
- to subjects in Part 2 with increased skin microfilariae at Month 18 compared to the number at Month 12 (rescue medication). In addition, at the 24-Month follow-up visit, ivermectin will be administered to subjects positive for microfilariae in the skin and/or eye after nodulectomy (post-study IVM).

3.5.4 Risks Associated with Epidemics

The presence of an epidemic, including for example COVID-19 or Ebola, could have an impact on the trial, trial subjects and personnel. This could potentially include subjects being in self-isolation/quarantine, limited access to public places, including hospitals, due to the risk of spreading infection, impact on the clinical trial itself and healthcare professionals being reassigned to critical tasks. Furthermore, subjects may be exposed to infection during screening activities in the communities or while they are at the investigational centre. In addition, there is the risk of study personnel transmitting infection to communities from which subjects will be recruited.

Mitigation steps to be taken include:

- Prior to initiation of recruitment, and during the trial, the Investigator and the Sponsor will assess the current potential risks associated with each aspect of the trial, based on the incidence of infections in the area of recruitment, the centre and national directives. The start of recruitment may be delayed if necessary or mitigation measures taken to protect study personnel and subjects.
- National and international guidelines will be followed during the trial to prevent the spread of infection (including testing site personnel and/or study subjects for COVID-19 when required by standard clinical care), and protective equipment will be provided in

accordance with the guidelines. Training will be provided to study personnel on standard precautions.
- Specific risk communication and education activities on national preventive directives on COVID-19 will be implemented for subjects as well as study personnel.
- If travel to and from the centre is blocked, the trained community contact persons in each recruitment area will ensure basic follow-up of subjects including supporting access to local medical assistance while keeping remote contact with the investigational centres.

Subjects with significant co-morbidities will not be included in the trial. The In-House Periods will also ensure that subjects will not be discharged back to their communities after the treatment period unless they are healthy. These measures will minimise the safety risks to subjects during follow-up, if visits are interrupted due to travel restrictions.

4 Study Objectives

4.1 Primary Objectives

The primary objectives are to:

Part 1:

- determine whether treatment with ABBV-4083 or ABBV-4083 + albendazole effectively depletes *Wolbachia* bacteria in adult female worms at Month 6 by immunohistology;
- establish the superiority of ABBV-4083 + albendazole to each drug alone according to the depletion of *Wolbachia* bacteria in adult female worms at Month 6 by immunohistology

Part 2:

- determine whether treatment with ABBV-4083 or ABBV-4083 + albendazole effectively eliminates microfilariae from the skin at 24 months.
- if superiority of 7-day treatment with ABBV-4083 + albendazole to 7 days of ABBV-4083 is not established in Part 1, the Alternate Scenario of Part 2 (see Section 3.3) has the additional objective to establish that a combination of ABBV-4083 + albendazole is superior to ABBV-4083 alone by combining data from Parts 1 and 2.

4.2 Secondary Objectives

4.2.1 Key Secondary Objectives for Part 2

The key secondary objectives for Part 2 are to determine:

- whether ABBV-4083 or ABBV-4083 + albendazole demonstrates a macrofilaricidal effect at 24 months;
- whether ABBV-4083 or ABBV-4083 + albendazole inhibits embryogenesis in adult female worms at 24 months.

4.2.2 Other Secondary Objectives

The other secondary objectives are to assess:

Part 1:

- the safety and tolerability of ABBV-4083 or ABBV-4083 + albendazole in subjects with *O. volvulus*;

- whether ABBV-4083 or ABBV-4083 + albendazole will sterilise the adult female worm and/or have a macrofilaricidal effect at Month 6;
- the effects of ABBV-4083 or ABBV-4083 + albendazole on skin microfilariae at all time-points;
- the effects of ABBV-4083 or ABBV-4083 + albendazole on microfilariae in nodular tissue at Month 6;
- whether ABBV-4083 or ABBV-4083 + albendazole depletes *Wolbachia* bacteria in adult worms assessed by PCR at Month 6.

Part 2:

- the safety and tolerability of ABBV-4083 or ABBV-4083 + albendazole in subjects with *O. volvulus*;
- the effects of ABBV-4083 or ABBV-4083 + albendazole with or without ivermectin at Month 6 on skin microfilariae at all applicable timepoints;
- the effects of ABBV-4083 or ABBV-4083 + albendazole with or without ivermectin at Month 6 on microfilariae in nodular tissue at 24 months;
- whether ABBV-4083 or ABBV-4083 + albendazole depletes *Wolbachia* bacteria in adult worms assessed by immunohistology and PCR at 24 months.

4.3 Exploratory Objectives for Parts 1 and 2

The exploratory objectives for both Parts 1 and 2 are to assess:

- whether ABBV-4083 or ABBV-4083 + albendazole depletes *Wolbachia* bacteria in microfilariae;
- the effects of ABBV-4083 or ABBV-4083 + albendazole on eye microfilariae;
- the pharmacokinetic (PK) parameters of ABBV-4083 and albendazole sulfoxide (the active metabolite of albendazole) in subjects;
- the relationship of PK parameters of ABBV-4083 and albendazole sulfoxide and efficacy and/or safety;
- the effects of ABBV-4083 or ABBV-4083 + albendazole on clinical outcomes:
  - itching and skin disease;
  - ocular onchocercal disease.

5 Study Endpoints

5.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

Part 1:

- the status of each live female adult worm as without *Wolbachia* endobacteria or not, as assessed by immunohistology of nodules collected after nodulectomy at 6 months;

Part 2:

- the status of each subject as without skin microfilariae or not at 24 months, assessed across all skin snips in each subject.

5.2 Secondary Efficacy Endpoints

5.2.1 Key Secondary Efficacy Endpoints in Part 2

The key secondary efficacy endpoints in Part 2 are:

- the proportion of live female adult worms per subject assessed by histological examination of all nodules collected after nodulectomy at Month 24;
- the proportion of live female adult worms with only degenerated embryos in uterus per subject as assessed by histological examination of nodules collected after nodulectomy at Month 24 out of all judgeable worms with embryos in uterus (normal or degenerated).

5.2.2 Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

Part 1:

- the proportion of live female adult worms with only degenerated embryos in the uterus per subject after nodulectomy at Month 6;
- the proportion of live female adult worms out of all female adult worms per subject after nodulectomy at Month 6;
- the absence of microfilariae in nodular tissue per subject after nodulectomy at Month 6;
- the status of each subject as without skin microfilariae or not at Months 3 and 6;
- the reduction in skin microfilarial density (defined as the mean number of microfilariae/mg per subject) at Months 3 and 6 compared to baseline;
- the status of each live adult worm as without *Wolbachia* endobacteria or not, as assessed by PCR at Month 6.

Part 2:

- the status of each subject as without skin microfilariae or not at all time-points other than Month 24;
- the reduction in skin microfilarial density (defined as the mean number of microfilariae/mg per subject) at all time-points compared to baseline;
- the absence of microfilariae in nodular tissue per subject after nodulectomy at Month 24;
- the status of each live adult female worm as without *Wolbachia* endobacteria or not, assessed by immunohistology at Month 24;
- the status of each live adult worm as without *Wolbachia* endobacteria or not, as assessed by PCR at Month 24.

5.3 Exploratory Endpoints in Parts 1 and 2

The exploratory endpoints are:

- the absence of *Wolbachia* in skin microfilariae per subject by PCR at all timepoints;
- the decline in number of *Wolbachia* (assessed by PCR) in skin microfilariae per subject at all timepoints compared to baseline;
- microfilaria levels in the cornea and anterior chamber per subject, at all timepoints when ophthalmological assessments are performed;

- the presence, severity and clinical evolution of onchocerciasis ocular disease and onchocerciasis skin disease in each subject at all time-points when ophthalmological or skin examinations are performed.

5.4 Additional Endpoint in Alternative Scenario in Part 2

The additional combination rule endpoint in Alternative scenario in Part 2 is:

- the proportion of live female adult worms without *Wolbachia* endobacteria assessed by immunohistology of nodules collected after nodulectomy at 6 months to compare ABBV-4083 + albendazole to 7 days of ABBV-4083.

5.5 Safety and Tolerability Endpoints in Parts 1 and 2

The safety and tolerability endpoints are:

- AE assessment (all reported AEs);
- physical and skin examination findings;
- vital signs;
- 12-lead ECG;
- clinical laboratory parameters: haematology, biochemistry, urine analysis;
- ophthalmological examination findings.

5.6 PK and PK/PD Endpoints in Parts 1 and 2

The PK and PK/PD endpoints are:

- ABBV-4083 and albendazole sulfoxide AUC_{tau}, C_{max}, C_{min}, CL and $t_{½}$. Time above given concentrations may also be estimated;
- the relationship between the presence or absence of *Wolbachia* in female adult worms in each subject at Month 6 with respect to ABBV-4083 and albendazole sulfoxide pharmacokinetic parameters;
- the relationship between the status of adult female worms at Month 24 with respect to ABBV-4083 and albendazole sulfoxide pharmacokinetic parameters;
- the relationship between the presence or absence of skin microfilariae at Month 24 with respect to ABBV-4083 and albendazole sulfoxide pharmacokinetic parameters;
- The relationship between the reduction in skin microfilarial density over time and ABBV-4083 and albendazole sulfoxide concentrations may be explored.

Additional relationships between the efficacy and safety endpoints and ABBV-4083 and albendazole sulfoxide concentrations may be explored.

6 Study Population

The inclusion and exclusion criteria are the same for Parts 1 and 2.

6.1 Inclusion Criteria

To be eligible for the study, subjects must satisfy all of the following inclusion criteria.

1. Written, signed (or thumb-printed) and dated informed consent, after having the opportunity to discuss the study with the Investigator or a delegate.

2. Men and women with *Onchocerca volvulus* infection, 18 to 65 years of age inclusive at time of Screening:
   i. Presence of at least one excisable subcutaneous nodule/onchocercoma detected on palpation;
   ii. *O. volvulus* infection diagnosed by skin snip method: documented mf-positivity on skin assessment on at least 2 out of 4 skin snips.
3. Body weight ≥ 40 kg at Screening.
4. For women of child-bearing potential (WOCBP), (see Section 8.2), acceptance of the requirement to use a highly effective form of birth control (see Section 8.2 and Appendix 7) effective from Day 0 until at least 1 month after the final intake of IMP (Part 1: day 43; Part 2: 1 month after the administration of ivermectin or matching placebo at the Month 6 visit). Choice of birth control method must be clearly documented.

6.2 Exclusion Criteria

Subjects must not satisfy any of the following exclusion criteria.

1. Participation in any studies other than purely observational studies within 3 months prior to Screening, or during the trial, or within 5 times the half-life of the drug tested in the previous clinical trial[*] or is currently in the follow-up period for any clinical trial.
2. Any vaccination within 4 weeks prior to IMP administration.
3. Acute infection and/or febrile illness requiring therapy within 14 days prior to IMP administration.
4. Administration of medication or herbal preparations as follows:
   i. Administration of any medication (with the exception of diclofenac, paracetamol, ibuprofen and aspirin) or herbal preparation within 14 days prior to IMP administration;
   ii. Use of strong CYP3A inhibitors or inducers including but not limited to ritonavir, ketoconazole, rifampicin, phenytoin, phenobarbital, carbamazepine, cimetidine within 14 days or 10 half-lives, whichever is longer, prior to IMP administration.
   iii. Use of other drugs known to interact with albendazole i.e. praziquantel, theophylline or dexamethasone, within 14 days or 10 half-lives, whichever is longer, prior to IMP administration;
   iv. 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-week course;

   and / or
   - any other anti-*Wolbachia* treatments i.e. minocycline, rifapentine or rifampicin, ≤ 1 year prior to IMP administration: more than 2-week course;

[*] Whichever is longer (time calculated relative to the last intake in the previous clinical trial.

and / or
- moxidectin, ≤ 2 years prior to IMP administration;

v. Other preventive chemotherapy, e.g. as part of an MDA program, within 14 days prior to IMP administration;

5. Requirement for and inability to avoid ivermectin during the first 6 months after IMP administration. Requirement for albendazole during the first 28 days after IMP administration or more than one dose per year thereafter given in MDA;
6. Presence of any of the following at Screening, that could interfere with the objectives of the trial or the safety of the subject, in the opinion of the Investigator:
   i. Clinically significant abnormal physical and/or neurological examination or laboratory findings;
   ii. Any clinically significant medical condition, including, but not limited to significant acute or chronic liver or kidney condition or cardiovascular disease, active infection, current or previous epilepsy, known human immunodeficiency virus (HIV) infection, disclosed by review of medical history or concomitant medication;
7. Ophthalmological history or conditions that could interfere with the objectives of the trial or compromise the safety of the subject in the opinion of the Investigator, assessed at Screening, including the following (subject will be excluded if any of the criteria are met for either eye):
   i. Inflammatory eye disease, glaucoma, severe uveitis; evidence of retinal cysticercosis;
   ii. History of surgery for glaucoma;
   iii. Severe keratitis, and/or cataracts that interfere with visualisation of the posterior segment of the eye;
   iv. Evidence of an increased risk of acute glaucoma, based on examination of anterior chamber;
   v. Evidence of ocular media opacity, including lens opacity and vitreous opacities, that make difficult ocular examination in the opinion of the investigator;
   vi. Evidence of retinal or optic nerve pathology, including age-related macular degeneration;
   vii. Severe visual impairment (best corrected or pinhole visual acuity worse than 6/60 metres), severe reduction of peripheral visual fields (greater than grade 3 on Frequency Doubling Technology) or blindness;
   viii. Any microfilariae identified in the posterior segment of the eye or more than 50 microfilariae in the anterior segment of one eye.
8. History of drug or alcohol abuse within 6 months prior to IMP administration.
9. Use of alcohol within 48 hours and/or use of drugs of abuse within 15 days before IMP administration.
10. Clinically significant history of cardiac abnormality, and/or relevant pathological abnormalities in the ECG in the screening period, such as atrioventricular block (PR interval > 240 msec), or prolongation of the QRS complex > 120 msec or QTcF interval > 450 msec.

11. Abnormal laboratory test results at Screening, defined as:
    i. Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and/or alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT > 2 × upper limit of normal (ULN[*]) and/or total bilirubin > 1.5 x ULN[*];
    ii. Serum potassium < lower limit of normal[*];
    iii. Serum creatinine > ULN[*] and estimated glomerular filtration rate (using the Modification of Diet in Renal Disease equation[73]) < 60 mL/min.
12. History of severe drug allergy, non-allergic drug reactions, severe adverse reaction to any drug, or multiple drug allergies.
13. Known hypersensitivity to any ingredient of the IMPs, including the active ingredient of ABBV-4083, macrolides, albendazole or to ivermectin or to any medication used during the study (e.g. for eye examination).
14. Blood donation within 8 weeks prior to Screening or blood transfusion received within 1 year prior to Screening.
15. Coincidental infection with high *Loa loa* load (> 8000 microfilariae/mL) at Screening.
16. Current hyperreactive onchodermatitis or severe manifestation due to onchocerciasis.
17. Any other past or current condition that the Investigator feels would exclude the subject from the study or place the subject at undue risk.
18. For women of child-bearing potential (WOCBP): pregnant (based on date of last menstrual period, and pregnancy test prior to first intake of IMP) or breastfeeding.
19. Unwilling or unable to comply with the requirements of the study protocol for the entire duration of the study, in the opinion of the Investigator.
20. Unable to participate in the study as per local law, if applicable.

6.3 Rationale for Study Population

Since the aim of the study is to assess the safety, tolerability, PK and efficacy of ABBV-4083 and ABBV-4083 + albendazole in subjects with onchocerciasis, it will be performed in an adult Sub-Saharan subject population infected with *O. volvulus* with detectable skin microfiladermia and palpable onchocercomata (nodules), which constitutes the future target population.

6.4 Subject Identification

All subjects will be assigned a unique identification number by the interactive response technology (IRT) system at the Screening visit. For subjects who rescreen, the Screening number assigned by the IRT at the initial Screening visit should be used. For subjects who comply with the entry criteria and are randomised, the IRT will assign a randomisation number that will encode the subject's treatment group assignment according to the randomisation

[*] Using the laboratory reference ranges defined for the study.

schedule generated by the Sponsor or Designee. It will be used only to determine the treatment assignment for each subject upon unblinding.

6.5 Discontinuation and Withdrawal Criteria

As a general principle, all subjects who receive at least one dose of IMP should continue participation in the trial, unless they withdraw consent. This is also to ensure follow-up of any adverse event, including documentation of its outcome.

The Investigator must consult with the Sponsor in all cases of interruption or discontinuation of the IMP, or withdrawal from the trial.

6.5.1 Screening Failure

A subject who discontinues study participation prematurely for any reason after s/he has signed the study main informed consent and undergone screening assessments, but before randomisation, is regarded as a "screening failure".

Subjects regarded as screening failures are not permitted to re-enter the screening process at a later time-point, except under the circumstances listed below.

- The inclusion and/or exclusion criteria preventing the subject's initial attempt to participate have been changed via protocol amendment;
- The subject failed the initial screening because the required wash-out period (as described in the exclusion criteria) had not been completed after prior treatment, or the required period after excluded procedures or substance use had not been completed, on a case-by-case basis, if agreed by the sponsor;
- The subject had successfully passed the initial screening, but the 8-week screening period expired before s/he could receive the IMP;

Subjects who re-enter the screening process must sign a new main informed consent form (ICF) and will keep the same screening number. Up to two re-screenings are allowed.

6.5.2 Interruption or Discontinuation of IMP

If treatment with the IMP is interrupted for any reason, the decision to resume treatment will be taken by the Investigator. The aim is to complete the treatment course, assuming it is safe to do so.

The IMP *must* be permanently discontinued if any of the following occurs:

- at subject's request. At any time during the study and without giving reasons, a subject may decline to take the IMP. The subject will not suffer any disadvantage as a result;
- positive pregnancy test

The IMP *may* be discontinued if any of the following occurs:

- if continuation of the IMP would be harmful to the subject's well-being, in the opinion of the Investigator;
- at the specific request of the Sponsor and in liaison with the Investigator, for example in the event of safety concerns;
- if the subject develops conditions that would have prevented his/her inclusion in the study according to the in-/exclusion criteria. The Investigator will decide in consultation with

the Sponsor, taking into account safety, and whether this is a conflict with the study objectives.

The reason and date for IMP discontinuation will be recorded in the source documents and electronic case report form (eCRF). Subjects who discontinue the IMP should continue participating in the study off the IMP with continued assessments as per the Schedule of Events.

6.5.3 Withdrawal from the Trial

Subjects *must* be withdrawn from the trial if any of the following occurs:

- at subject's request (withdrawal of consent). At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

Subjects *may* be withdrawn from the study if any of the following occurs:

- if continuation of the study would be harmful to the subject's well-being, in the opinion of the Investigator;
- at the specific request of the Investigator, or the Sponsor in only very exceptional circumstances and in liaison with the Investigator, for example in the event of safety concerns for the subject or others;
- in the event of premature termination of the study (see Section 12).

If a subject withdraws consent, no further evaluations should be performed, and no attempts should be made to collect additional data, with the exception of safety data, which should be collected if possible and only with the subject's consent. The Sponsor may retain and continue to use any data collected before withdrawal of consent. However, if the subject consents to follow-up but asks the Investigator to destroy all identifiable samples taken from the subject and/or not enter in the eCRF results of the follow-up examinations, the Investigator will comply with the subject's requests.

If a subject withdraws from the study, the reason and date must be noted in the source documents and in the eCRF.

The Investigator should inquire about the reason for withdrawal, and conduct an Early Termination visit as soon as possible, if the subject agrees (see Schedules of Events in Appendix 1 and Appendix 2).

If a subject withdraws from the study due to an AE, all measures must be taken to clearly document the outcome of the AE.

6.5.4 Lost to Follow-up

A subject will be considered lost to follow-up if s/he can no longer be contacted by the study personnel (see also the Study Operations Manual).

Before the subject can be considered as lost to follow-up, the study personnel must make every effort to re-establish contact with the subject as soon as possible to advise him/her of the importance of continuing in the study and to ascertain whether or not s/he wishes to and/or should continue in the study. In addition, every effort should be made to document subject status. The contact attempts should be recorded in the source documents and in a note in the Investigator Site File. If a subject is finally considered lost to follow-up, this must be noted in the source documents and on the eCRF.

6.5.5 Subject Replacement

Subjects who withdraw or are withdrawn from the study after randomisation will not be replaced.

7 Investigational Medicinal Products.

7.1 Test Investigational and Reference Medicinal Products

7.1.1 ABBV-4083 and Matching Placebo

The test IMP, i.e. the Sponsor's active compound under investigation in the study, is ABBV-4083, which will be administered alone or in combination with the test IMP albendazole.

The composition of the capsule of ABBV-4083 and matching placebo are shown in Table 2.

Table 2. Composition of ABBV-4083 and Matching Placebo

Generic name	ABBV-4083	Matching placebo
Dosage form	Capsule for oral administration	Capsule for oral administration
Dosage strength	100 mg	Not applicable
Composition	Contents: microcrystalline cellulose, dibasic calcium phosphate anhydrous, croscarmellose sodium, hydroxypropyl cellulose, colloidal silicon dioxide, magnesium stearate Capsule: light grey, opaque Capsule shell: gelatine, titanium dioxide, iron oxide black	Contents: microcrystalline cellulose Capsule: light grey, opaque Capsule shell: gelatine, titanium dioxide, iron oxide black

In Part 1, ABBV-4083 will be administered at the dose of 400 mg, i.e. four 100-mg capsules. If toxicity criteria are met (see Section 3.5.2), the dose of ABBV-4083 may be reduced to 300 mg, i.e. three 100-mg capsules, or matching placebo.

The dose(s) of ABBV-4083 in Part 2 will be confirmed based on data from Part 1, i.e. up to two treatment arms from Part 1 that are likely to demonstrate high efficacy at Month 24 and safety will be selected. The choice will take into consideration feasibility to use the regimen as potential future treatment.

7.1.2 Albendazole and Matching Placebo

Albendazole will be administered at the dose of 400 mg, i.e. one over-encapsulated 400-mg tablet, or matching placebo.

The composition of the over-encapsulated tablet of albendazole and matching placebo are shown in Table 3.

Table 3. Composition of Albendazole and Matching Placebo

Generic name	Albendazole	Matching placebo
Dosage form	Capsule for oral administration	Capsule for oral administration
Dosage strength	400 mg	Not applicable
Composition	Tablet: Lactose, microcrystalline cellulose, maize starch,	Contents: microcrystalline cellulose Capsule: Swedish orange, opaque

	croscarmellose sodium, povidone. sodium lauryl sulphate, sunset yellow lake, sodium saccharin, magnesium stearate, orange flavour, vanilla favour, passion fruit flavour Capsule: Swedish orange, opaque Capsule shell: gelatine, titanium dioxide, red iron oxide	Capsule shell: gelatine, titanium dioxide, red iron oxide

Source: SmPC for Zentel®.[57]

Two active doses / dose regimens from Part 1 will be selected for Part 2, based on all available data, including safety and tolerability of ABBV-4083 and ABBV-4083 + albendazole, *Wolbachia* depletion, embryonic disruption and an exploratory surrogate marker, microfilaria *Wolbachia*, measured at Months 3 and 6.

7.1.3 Ivermectin and Matching Placebo

Ivermectin or matching placebo will be given over-encapsulated in Part 2.

The composition of the tablet of ivermectin and matching placebo are shown in Table 4.

Table 4. Composition of Ivermectin and Matching Placebo

Generic name	Ivermectin	Matching placebo
Dosage form	Tablet, over-encapsulated	Visually-matched capsule containing inactive excipients
Dosage strength	3 mg	Not applicable
Composition	Microcrystalline cellulose, pregelatinized maize starch, magnesium stearate, butylated hydroxyanisole and Citric acid anhydrous Capsule shell: gelatin and titanium dioxide	Microcrystalline cellulose, pregelatinized maize starch, magnesium stearate, butylated hydroxyanisole and citric acid anhydrous Capsule shell: gelatin and titanium dioxide

Source: SmPC for Stromectol®2010. [65]

Ivermectin will be given at the approved single oral dose of 150 µg/kg bw. This corresponds to between 2 and 4 capsules per subject depending on the subject's weight), for subjects weighing up to 84 Kg. Subjects weighing > 84 Kg may receive additional tablets (see Table 5). Each over-encapsulated ivermectin tablet contains 3 mg ivermectin.

Table 5. Dose of Ivermectin by Body Weight

Body weight (kg)	Dose (mg)	Number of tablets
26-44	6	2
45-64	9	3
65-84	12	4
≥85		150 µg/kg

Source: SmPC for Stromectol® 2010.[65]

7.2 IMP Supply and Storage

ABBV-4083 and matching placebo, over-encapsulated albendazole and matching placebo will be supplied by AbbVie. The clinical supplies will be packaged and labelled by AbbVie. Final assembly of subject treatments, packaging, labelling and batch release will be performed by AbbVie.

In Part 2, Month 6 over-encapsulated intact commercially available ivermectin tablets and visually-matched placebo capsules containing inactive excipients will be supplied and packaged by AMATSI Group. Final assembly of subject treatments, packaging, labelling and batch release will also be performed by AMATSI Group.

All IMPs will be labelled in accordance with the requirements of local laws and regulations. The labelling text will be approved according to the Sponsor's agreed procedures, and a copy of the labels will be made available to the regulatory authorities and investigational centre upon request.

Packaging, labelling and storage conditions of the IMPs, as well as supply of the IMPs to the investigational centre will be described in the Pharmacy Manual.

At the investigational centre the IMPs will be stored in a locked cabinet, inaccessible to unauthorised personnel.

ABBV-4083 and matching placebo are to be stored protected from light, at a temperature between 2 °C and 30 °C and should not be frozen.

Albendazole and matching placebo are to be stored at a temperature between 2 °C and 30 °C and should not be frozen.

Over-encapsulated ivermectin tablets and matching placebo are to be stored at a temperature not exceeding 30 °C.

The supplies of ABBV-4083, albendazole and ivermectin for the study must not be used for purposes other than the present protocol. The Investigator and the study personnel staff may not, under any circumstances, provide other healthcare workers or services with the IMPs, or allow the IMPs to be used other than as described in this protocol without prior written approval from the Sponsor.

A system of numbering in accordance with the requirements of Good Manufacturing Practice (GMP) will be used for the IMPs, ensuring that each dose of IMP can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the Sponsor's suppliers for the IMPs.

A complete record of batch numbers and expiry dates of all IMPs as well as the labels will be maintained in the Sponsor's study file.

7.3 IMP Assignment and Administration

7.3.1 IMP Assignment and Administration in Part 1

7.3.1.1 IMP Assignment in Part 1

In Part 1, the IMP will be randomly assigned. A total of 150 subjects will be recruited and centrally and continuously randomised under double blind 1:1:1:1:1 into one of five parallel groups (Arms A, B, C, D and E), based on dosing regimen, until group size is achieved. Subjects

will be stratified by the number of operable sites with onchocercomata. There will be two strata, i.e. one site and more than one site.

7.3.1.2 IMP Administration in Part 1

The IMP ABBV-4083 will be administered as 100-mg capsules or matching placebo capsules.

The IMP albendazole will be administered as over-encapsulated 400-mg tablets or matching over-encapsulated placebo .

Subjects will receive a maximum of 5 capsules per day for 14 days. Depending on the treatment arm allocation, subjects will receive four ABBV-4083 capsules (400 mg) or matching placebo + one over-encapsulated albendazole tablet (400 mg) or matching placebo, once a day, from Day 0 to Day 6, followed by four ABBV-4083 capsules (400 mg) or matching placebo, once a day, from Day 7 to Day 13.

The IMPs will be administered once daily by the oral route and are to be taken with food (see Section 9.2.8 for details).

The IMP will be administered at the investigational centre at approximately the same time each morning, and intake of the IMP will be directly observed by the study personnel.

7.3.2 IMP Assignment and Administration in Part 2

7.3.2.1 IMP Assignment in Part 2

In Part 2, there will be four treatment arms. The two study arms of the shortest treatment duration in Part 1 that are likely to demonstrate high efficacy at Month 24 (based on Part 1 efficacy results and historical studies with doxycycline) and safety will be selected as active arms for Part 2. In order also to assess an additional effect of a dose of ivermectin at Month 6, participants will be into four groups stratified by the number of operable sites with onchocercomata (one site, > 1 site) and by mean skin mf (≤ 5 mf/mg, > 5 mf/mg) at Screening, with two arms receiving the same ABBV-4083 or ABBV-4083 + albendazole regimen but one receiving ivermectin at Month 6 and the other receiving ivermectin matching placebo.

In the Base Scenario, subjects will be randomly assigned 2:2:2:1 under double blind to Arms K, L, M and N1.

In the Alternative Scenario, subjects will be randomly assigned 1:1:1:1 under double blind to Arms K, L, M and N2.

7.3.2.2 IMP Administration in Part 2

The IMP ABBV-4083 will be administered as 100-mg capsules or matching placebo capsules.

The IMP albendazole will be administered as over-encapsulated 400-mg tablets or matching over-encapsulated placebo .

The IMPs ABBV-4083, albendazole and both matching placebo will be administered once daily by the oral route and are to be taken with food (See Section 9.2.8 for details).

The IMP ivermectin or matching placebo will be administered at the approved single oral dose of 150 µg/kg body weight per Table 5 as a single administration at Month 6. It will be administered to subjects on fasting conditions with water.

All IMPs will be administered at the investigational centre at approximately the same time each morning, and intake of the IMP will be directly observed by the study personnel.

7.4 Blinding

7.4.1 Blinding Measures

In both parts of the study, the IMPs will be administered under double-blind conditions. To that end, ABBV-4083 and matching placebo capsules, as well as albendazole over-encapsulated tablets or matching placebo capsules will be identical in appearance, i.e. size, shape and colour, taste and smell. In Part 2, over-encapsulated ivermectin tablets and matching placebo capsules will be identical in appearance, taste and smell. The packaging and labelling will be designed to maintain blinding to the Sponsor and study personnel, as well as to subjects. The study data will remain blinded until each planned database locks of the study, and authorisation of data release according to standard operating procedures.

The Investigator, as well as clinical, pharmacy, and laboratory personnel, and the Sponsor, including statistics and data management personnel and the study monitor, will remain blinded during the study, excluding those individuals, intentionally designated as unblinded and described below, so as not to potentially introduce bias, unless safety concerns necessitate unblinding by the Investigator, i.e. if knowledge of the IMP administered is useful for the best medical care of an SAE (see Section 7.4.2).

A copy of the randomisation codes in each part of the study will be kept under the management of dedicated unblinded personnel designated by the Sponsor, and access strictly limited to those minimally designated unblinded staff directly involved in activities requiring access to the randomisation code, e.g. staff directly involved in pharmacovigilance for expedited safety reporting only, bioanalytical processes and PK evaluation, packaging and labelling service providers, etc., plus quality control activities (by independent personnel) related to these activities.

The emergency procedures for revealing medication codes are specified in Section 7.4.2.

7.4.2 Unblinding Measures

If emergency unblinding is required in the interest of the safety of a subject, an Investigator will discuss the matter with the Sponsor before contacting IRT to break the blind for that subject, unless, in a medical emergency, when the Principal Investigator or delegate may contact IRT to break the blind for that subject without prior consultation with the Sponsor. Designated Sponsor personnel will be notified via IRT that unblinding occurred but with no information on the treatment allocation. In the event of emergency unblinding by the Principal Investigator or delegate, there will be a process in place to prevent unnecessary unblinding of others to the treatment allocation. This will include documenting the circumstances together with justification and the actions taken following the unblinding, using a specific form with restricted access.

In compliance with applicable regulations, in the event of unblinding for safety reporting by the Sponsor to the regulatory authorities and ethics committee(s), a process will be in place via the IRT system to prevent unblinding of the clinical team.

If the randomisation code is broken by the Investigator, the reason and date will be fully documented and entered in the source documents and eCRF (in a blinded manner).

The DSMB may exceptionally request unblinding of certain subject(s), e.g. in case of a major safety concern, but only if absolutely necessary, and always in accordance with the DSMB Charter.

The study data will be unblinded after database lock in Part 1 and in Part 2.

7.5 IMP Logistics and Accountability

All IMPs will be stored at the investigational centres in accordance with GCP and GMP requirements and the instructions given by the Sponsor and will be inaccessible to unauthorised personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the Sponsor's study file; the centre-specific elements of this information will be available in the Investigator Site File. On the day of receipt, the responsible study personnel will confirm receipt of the IMPs per the instructions supplied. The personnel will use the IMPs only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the IMPs must be properly documented according to the Sponsor's agreed and specified processes and procedures.

Written instructions on IMP destruction will be made available to affected parties as applicable, and in accordance with any requirements of the regulatory authority.

7.6 Treatment Compliance

The IMPs will be administered by the study personnel. Treatment compliance will therefore be ensured by direct observation. Treatment intake will be recorded in the eCRF. In addition, in both parts of the study, ABBV-4083 and albendazole levels will be measured in the blood at regular time-points (see Schedules of Events in Appendix 1 and Appendix 2).

8 Non-study Medication

8.1 Prior and Concomitant Medication

The prior medication listed below will be recorded in the source documents and eCRF. See Section 6.2 for exclusion criteria based on concomitant medication.

- All prior anthelminthic treatments or medication given for onchocerciasis including ivermectin or albendazole alone or in combination, doxycycline, minocycline, rifampicin, rifapentine, moxidectin, praziquantel or mebendazole, including date of last intake.
- Doxycycline for other indications, within 1 year prior to IMP administration
- Vaccinations, within 4 weeks prior to IMP administration
- All other prior medication, including contraceptives, and preventive chemotherapy, herbal preparations or food supplements taken within 1 month before the start of Screening at the investigational centre
- Other currently effective contraceptive medication or devices, including long-acting depot or implantable preparations containing sex hormones or intra-uterine devices, (see also Section 8.2)

From signature of ICF onwards, subjects will be instructed not to take any medications, traditional medicines or herbal preparations by themselves at any time during the study (with the exception, where relevant, of contraceptives allowed by protocol).

During the study, if the subject requires treatment, the Investigator should be informed and approve the proposed medication in line with the following instructions:

Throughout the entire study, the use of medication that may have an impact on the study objectives is not permitted.

- In addition, up to 24 hours after the final dose of IMP, no medication, including herbal remedies or food supplements and preventive chemotherapy (MDA), other than the IMPs, rescue medication and permitted medication described in this section is allowed unless absolutely necessary for treatment of AEs or the symptoms of onchocerciasis (see Appendix 8 for the list of prohibited medication during the trial).
- Permitted medications, as an exception, include:
  - diclofenac, paracetamol, ibuprofen, and aspirin
  - contraceptives (see Section 8.2) for WOCBP
  - topical drugs required for the eye examinations (e.g. mydriatic eye drops, anaesthetic drops)

The following information will be recorded (along with the details as specified in Section 9.3.1.3):

- Medications taken between signature of ICF and the end of study participation (see Section 3.4) must be recorded in the source documents and eCRF.
- Any medication used to treat an SAE at any time in the study must be recorded in the source document, eCRF and SAE reporting form.

8.2 Contraception/Birth Control

Women of child-bearing potential (WOCBP) must agree to use or continue to use a highly effective birth control method as defined by the EU Clinical Trial Facilitation Group and detailed in Appendix 7 until at least 1 month after the last intake of IMP (Part 1: day 43; Part 2: 1 month after the administration of ivermectin or matching placebo at the Month 6 visit).

Contraceptives permitted by local regulations will be used. The most recent depot injection or implant or hormonal intra-uterine device or oral contraceptives should have been administered at least 14 days prior to Day 0. If required, the Investigator can arrange for suitable highly effective contraception to cover the required period.

For WOCBP, details of the contraceptives used will be documented in the source documents.

The definition of WOCBP according to the Clinical Trial Facilitation Group will be used in the trial as follows: a woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months with no alternative medical cause.[74]

Contraception is not required for male subjects participating in the trial.

8.3 Ivermectin: Rescue Medication, Post-Study, Screening Failures

Ivermectin used as described in this section for rescue medication or post-study will be provided as a single oral administration at the approved dose of 150 µg/kg bw and is not an IMP, i.e. will not be presented as over-encapsulated tablets.

When ivermectin is administered at a follow-up or early termination visit, it must be administered only after completion of the procedures scheduled at that visit, and after confirmation of last menstrual period and a negative pregnancy test. Ivermectin will be administered to subjects under fasting conditions.

Subjects who fail screening in the communities or at the investigational centre will be referred to the National Program PNLMTN-CTP for MDA with ivermectin.

8.3.1 Rescue Medication in Part 1

In Part 1, ivermectin will be administered as rescue medication at any time during the study, at the investigator's discretion, to subjects with clinically significant worsening of symptoms and/or signs related to onchocerciasis.

8.3.2 Rescue Medication in Part 2

In Part 2, ivermectin will be proposed as rescue medication to all subjects with clinically significant worsening of symptoms and/or signs related to onchocerciasis at any time during the study and/or to subjects with increased mean number of skin microfilariae at Month 18, compared to the mean number at Month 12.

8.4 Post-study Ivermectin

In Part 1, ivermectin will be administered to all subjects at the 6-month follow-up visit.

In Part 2, ivermectin will be administered to any subjects positive for microfilariae in the skin or eye at the 24-month follow-up visit. In addition, all subjects will be advised to continue to participate in MDA in their communities.

In all parts of the trial, in the event of early termination, subjects will be offered ivermectin at the Investigator's discretion.

9 Study Procedures and Assessments

9.1 Conduct of Study Procedures and Assessments

The Schedule of Events for Part 1 is presented in Appendix 1.

The Schedule of Events for Part 2 is presented in Appendix 2. Schedule of Events in Part 2

Every effort should be made to ensure that protocol-required procedures and assessments are performed as described.

Permitted time windows related to days of scheduled visits are detailed in the Schedules of Events.

Examinations may be repeated in the event of a technical failure. This may require an additional out-patient visit if absolutely necessary.

In the event of certain AEs considered to be associated with the IMP, additional examinations to better interpret the AE may be conducted, including safety laboratory, PK, ophthalmological, physical, neurological and parasitological examinations.

However, it is anticipated that from time to time there may be circumstances outside the control of the Investigator that may make it unfeasible to perform the test. In those cases, the

Investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for the missed test in the source documents, will document any corrective and preventative actions that were taken to ensure that the required procedures were adhered to as soon as possible, and record this as a protocol deviation. The Sponsor study team must be informed of these incidents in a timely manner, and, if required in the country, they must be reported to the regulatory authorities and ethics committee(s).

9.2 Description of Study Periods

Unless otherwise specified, the procedures and assessments listed in the following sections will be performed by or under the supervision of the Investigator.

9.2.1 Overview of Study Periods

An overview of the study periods in Part 1 is provided in **Figure 4** and for Part 2 in Figure 5.

Figure 4. Overview of Study Periods in Part 1

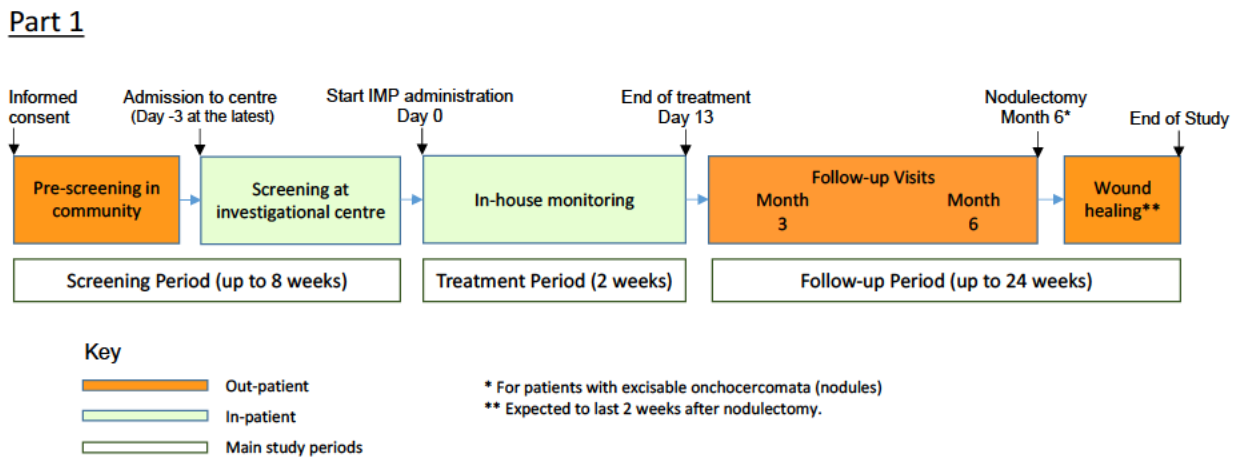
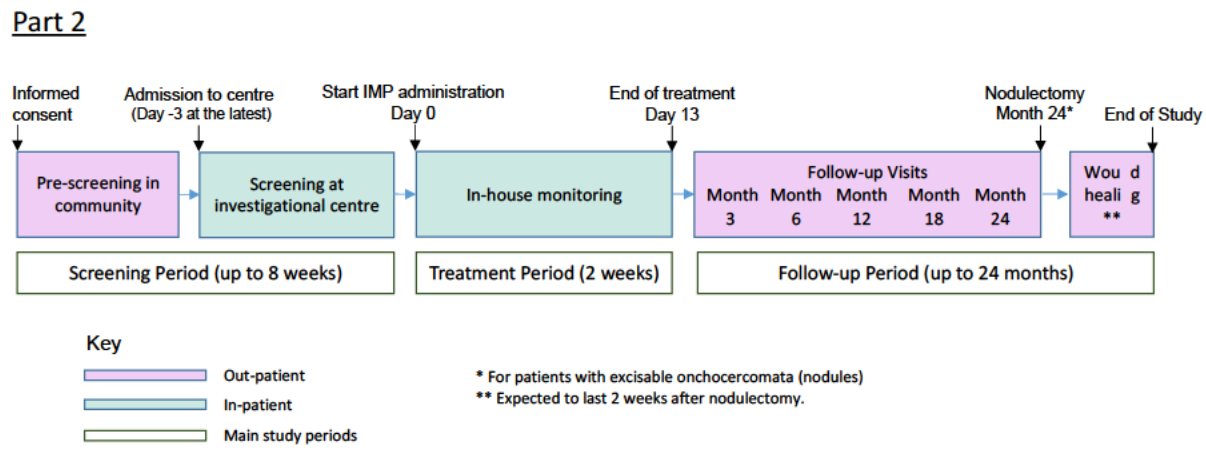


Figure 5. Overview of Study Periods in Part 2



Additional information can be found in the Schedule of Events (see Appendix 1 **Error! Reference source not found.**and Appendix 2. Schedule of Events in Part 2).

9.2.2 Screening Period

Informed consent will be collected before any study-specific procedures are performed. The procedure for obtaining informed consent is described in the Study Operations Manual.

Screening procedures will be performed, and the results will be assessed within 8 weeks prior to the first IMP administration.

Screening is likely to take place in two parts.

Pre-screening will usually take place in the subjects' communities to confirm the diagnosis of onchocerciasis and eligibility to participate in the study and will be performed by trained study personnel authorised by the investigator. A specific pre-screening ICF will be used to review and explain to the subjects the procedures that will be performed during the pre-screening phase. Subjects who are eligible based on the pre-screening will be invited to participate in the study. A separate ICF will be used to collect the subject's consent to participate in the main study. After signature of the ICF for the main study, the subject will be invited for further screening at the investigational centre.

The remaining procedures and assessments not performed during the initial screening in the community or which are out of window, as specified in the Schedule of Events, will be performed at the investigational centre

Screening procedures may be performed the same day as signing of the ICF or a few days later, however, no screening procedures will be performed until the corresponding ICF has been signed. However, in case of re-screening, the procedures that were performed during the previous screenings, which didn't lead to the exclusion of the subject and which are still within the allowed window as per the Schedules of Events for Part 1 and Part 2 (see Appendix 1 and Appendix 2) won't be repeated, unless deemed necessary by the investigator. If the initial screening procedures start on the same day as the subject signs the ICF, the time of the subject's signature will be recorded on the subject's ICF and medical file. Some initial screening procedures may be performed during that visit. This will depend on the centre-specific recruitment procedures and logistic capacity (see Study Operations Manual for centre-specific information).

9.2.3 Randomisation

Eligible subjects will be centrally randomised using an IRT system after checking inclusion and exclusion criteria and before the first intake of the IMP. Randomisation may take place on Day -1, provided all the required examination results are available to assess subject eligibility in relation to the inclusion and exclusion criteria.

Randomisation in the trial is described in the Study Operations Manual.

9.2.4 Treatment Period

The procedures to be performed each day during the treatment period are presented in the Schedules of Events for Part 1 and Part 2 (see Appendix 1 and Appendix 2) and a flow-chart is provided in the Study Operations Manual, with a day-to-day description of the various visits.

It is important that each procedure for an individual subject is performed at around the same time each day throughout the treatment period.

Some procedures are to be performed before IMP administration and others after IMP administration (see below for details).

Note that not all procedures are to be performed at each study visit (see the Schedule of Events for information on which ones to perform).

9.2.4.1 Procedures routinely to be performed before IMP administration

- Collection of pre-dose AEs (see Section 9.3.4).
- Collection of pre-dose concomitant medications (see Section 8.1 and 9.3.1.3)
- Laboratory safety, including haematology, biochemistry and urinalysis (see Section 9.3.3.9.1)
- Pregnancy test in WOCBP (see Section 9.3.3.9.3)
- Collection of exploratory samples
- Pre-dose PK blood sampling (see Section 9.3.2)
- Vital signs (see Section 9.3.3.6)

The IMP must be administered to subjects with food (see Section 9.2.8), except for ivermectin or matching placebo at Month 6 in Part 2, which must be administered in the fasting state.

9.2.4.2 Procedures routinely to be performed after IMP administration

- Full or shortened symptom-directed physical examination (see Section 9.3.3.3)
- Brief neurological examination (see Section 9.3.3.4)
- Collection of post-dose AEs (see Section 9.3.4)
- Collection of post-dose concomitant medications (see Section 8.1 and 9.3.1.3)
- 12-lead safety ECG (see Section 9.3.3.8)
- Post-dose PK blood sampling (see Section 9.3.2)
- Ophthalmological examination (see Section 9.3.3.7)
- Skin snip (see Section 9.3.3.1.1)

9.2.5 Follow-up Period

All the procedures that need to be performed at every follow-up visits are listed in the Schedules of Events for Part 1 and Part 2 (see Appendix 1 and Appendix 2) and a flow-chart will be provided in the Study Operations Manual to indicate a description of the different visits.

9.2.6 Early Termination Visit

See also Section 6.5.

All of the procedures to be performed at the early termination visit (unless the subject withdraws consent for some or all, as described in Section 6.5) are listed in the Schedules of Events for Part 1 and Part 2 (see Appendix 1 and Appendix 2) and a flow-chart will be provided in the Study Operations Manual to describe the visit.

9.2.7 Accommodation

During the In-house Period, subjects in Part 1 and Part 2 will stay in or close to the investigational centre, which will be in or close to a hospital, for completion of screening, during the treatment, and for observation after the last intake.

Subjects will return to the centre for follow-up visits.

Subjects may remain in the investigational centre for nodulectomy. Overnight accommodation may be provided at other times, associated with study visits for logistical reasons or social reasons or in the event of technical issues.

9.2.8 Dietary and Lifestyle Guidelines in Parts 1 and 2

The dietary and lifestyle guidelines for subjects in Part 1 and Part 2 are presented in Table 6.

Table 6. Dietary and Lifestyle Guidelines - Part 1 and Part 2

Parameter	Guidelines
Grapefruit and grapefruit juice	Subjects will be instructed not to consume grapefruit from 7 days prior to IMP administration until 24 hours after the final intake of the IMP.
Alcoholic drinks	Subjects will be instructed: - not to consume alcohol from 48 hours prior to IMP administration until the end of the in-house period; - not to consume alcohol for 24 hours before each out-patient follow-up visit; - not to consume more than 3 units per day (1 unit = 250 mL of beer or 25 mL of spirits) at any time up to the 3-month visit; - to avoid excessive use of alcohol at all other times during the study.
Caffeinated drinks	No restriction
Smoking	Subjects will be instructed not to smoke from 24 hours prior to IMP administration until 24 hours after the last IMP administration.
Food and water intake	On the days when laboratory safety samples are collected, the subjects will fast for at least 8 hours prior to sample collection. During the in-house period, standard local meals will be provided at usual times designated by the Investigator. The meal contents will be recorded in the source documents and the timing with respect to IMP administration and that it was consumed will be recorded in the source documents and in the eCRF. IMP should be administered with food. Subjects will be allowed to drink water *ad libitum* at all times during the study.
Drugs of abuse	Subjects will be instructed these are prohibited throughout the study.
Driving and operating of machinery	No studies have been performed on ABBV-4083 or Albendazole regarding the effects on the ability to drive and use machines. Subjects will remain in or close to the research centre during the treatment period, however as a precaution they will be advised to avoid these activities between the first intake of IMP and up to 2 days after the last intake of the IMP.

9.3 Summary of Study Procedures and Assessments

9.3.1 Subject Characteristics

9.3.1.1 Demographic Data

The following demographic data items will be recorded in the eCRF:

- Year of birth and/or age;

- Sex;
- Ethnic origin;
- Body weight;
- Height.
- Town and/or district of residence.

9.3.1.2 Medical History

The following medical history items will be recorded:

- Relevant past medical history, including prior diseases with start and end dates, prior treatment with start and end dates (see Section 8.1);
- Surgical history, including indications and dates;
- Current medical history, including start date and grade of on-going conditions;
- Symptoms of onchocerciasis disease (ocular, skin, other).

9.3.1.3 Concomitant Medication

The following items for concomitant medication will be recorded:

- International non-proprietary name (i.e. generic name); dose, frequency, route of administration and indication;
- Start and stop dates

9.3.2 Pharmacokinetics and Pharmacodynamics

Blood samples for PK analyses of ABBV-4083 and albendazole sulfoxide, i.e. the active metabolite of albendazole, will be collected in Parts 1 and 2 at the time-points indicated in the Schedule of Events (see Appendix 1 and Appendix 2). A dry blood spot collection method will be used, for which detailed instructions will be included in the Laboratory Manual. The PK analyses will be performed using validated analytical methods. Since the PK calculations will be based on actual sampling, dosing times, and content of the meal provided with dosing, the data must be thoroughly documented in the subject's medical file and/or eCRF.

The PD effect of ABBV-4083 and of albendazole sulfoxide, the active metabolite of albendazole, on *Wolbachia* levels in female adult worms, status of female adult worm and skin microfilariae will be assessed in Parts 1 and 2 with regard to the PK parameters of ABBV-4083 and albendazole (see also Section 9.3.3.1).

9.3.3 Efficacy and Safety

9.3.3.1 Parasitology

9.3.3.1.1 Blood, Urine and Skin Snip Parasitology

The following assessments will be performed at Screening:

- In blood, testing for *Wuchereria bancrofti, Mansonella perstans* and *Loa loa*;
- In skin snips, testing for *Mansonella streptocerca,* and *O. volvulus*.

9.3.3.1.2 Microfilaria Levels in the Skin

A total of four skin snips will be taken at each time-point indicated in the Schedules of Events (see Appendix 1 and Appendix 2) to test for *O. volvulus* microfilariae and calculate skin microfilarial density. The presence of any microfilariae from other species, such as *Mansonella streptocerca*, will also be recorded.

The specimens will be collected from the iliac crests and calves using a corneoscleral punch. One punch will be used per subject, and punches will be sterilised between subjects. Each snip will be incubated overnight, then weighed. The microfilariae that have emerged from the skin snips in the wells during incubation will then be counted.

PCR will be used to assess the effect of the IMPs on *Wolbachia* bacteria in skin microfilaria.

Processing of samples will be in accordance with the laboratory's standard operating procedures, and additional information will be provided in the Laboratory Manual/Study Operations Manual.

9.3.3.1.3 Microfilaria Counts in the Cornea and Anterior and Posterior Segments of the Eyes

Microfilaria counts in the cornea and anterior and posterior segments will be assessed as part of the ophthalmological evaluations (see Section 9.3.3.7) in accordance with the procedures described in the Study Operations Manual.

9.3.3.1.4 Nodulectomy and Histological Assessment of Nodules

Nodulectomy will be performed under local anaesthesia using aseptic and standard surgical procedures.

The subjects will be scheduled for an operation date and will be transported from their community either the evening before or early in the morning. Following surgery, the subjects will usually stay overnight in the investigational centre, or longer for logistic reasons or if medically indicated, and the subjects will then return to their communities where a nurse will continue wound management for up to approximately 2 weeks.

Wound management will begin following the incision and continue until the wounds are completely healed. Subjects will be advised to stay off work for the first week post-surgery to promote wound healing. Sutures will be removed approximately 8 days post-nodulectomy.

Evidence of an effect on the macrofilariae and microfilariae will be obtained from histological examination of nodules excised at the time-points indicated in the Schedule of Events (see Appendix 1 and Appendix 2).

PCR will be used to assess the effect of the IMPs on *Wolbachia* bacteria in adult worms.

Removal of nodules and judgement of the adult worms will be performed according to published procedures.[75,76] Detailed instructions on processing and assessment of the nodules including PCR assessments will be included in the Laboratory Manual/Study Operations manual/standard operating procedures (SOPs).

9.3.3.2 Clinical Outcomes

In Parts 1 and 2, clinical outcomes of onchocerciasis ocular disease, onchocerciasis skin disease, and itching will be assessed at the time-points indicated in the Schedule of Events (see

Appendix 1 and Appendix 2) The assessments will take place during ophthalmological examinations (see Section 9.3.3.7) and skin examinations (see Section 9.3.3.5).

9.3.3.3 Physical Examination

A full physical examination, including height and weight (only at Screening) and a complete review of body systems will be performed at the time-points specified in the Schedule of Events (see Appendix 1 and Appendix 2). At some time-points, a shortened symptom-directed physical examination will be performed. Detailed instructions for the physical examination will be provided in the Study Operations Manual/SOPs.

9.3.3.4 Neurological Examination

A brief neurological examination will be performed at various time-points specified in the Schedules of Events (see Appendix 1 and Appendix 2). Detailed instructions for the short neurological examination will be provided in the Study Operations Manual/SOPs.

9.3.3.5 Skin Examination and Nodule Palpation

Specific onchocerciasis examinations will be performed at the time-points specified in the Schedules of Events (see Appendix 1 and Appendix 2).

Nodule Palpation will be conducted, with documentation of *Onchocerca* nodules.

Skin examinations will be conducted to document manifestations of onchocercal skin disease and itching, to assess clinical outcomes (see Section 9.3.3.2). The clinical classification and grading system of the cutaneous changes in onchocerciasis scale (modified) will be used.[77] Detailed instructions for the skin examination will be provided in the Study Operations Manual/SOPs.

9.3.3.6 Vital Signs

The following parameters will be assessed for vital signs with one measurement at each specified time-point (see Appendix 1 and Appendix 2).

- Supine systolic BP;
- Supine diastolic BP;
- Supine heart rate;
- Resting respiratory rate;
- Temperature.

Measurements will be repeated if values are outside of the ranges defined in the Study Operational Manual. If the result of the repeat measurement is still out of range, it will be assessed for clinical significance and, in accordance with the instructions in Section 9.3.4.2, may be reported as an AE.

9.3.3.7 Ophthalmological Examination

Ophthalmological assessments will be performed by a specialist at the time-points specified in the Schedule of Events (see **Appendix 1** and **Appendix 2**). The assessments will include past ocular history, ocular symptoms, ocular examinations including ocular alignment and mobility

and pupillary response, visual function (visual acuity, visual field, colour vision), slit lamp examination of anterior and posterior segments and intraocular pressure measurement and fundus photography.

Motile and non-motile microfilariae in the cornea, and the anterior and posterior segments, and onchocercal corneal punctate opacities will be counted.

Subjects will be informed that they will need to bring their distance glasses (if applicable) and their near vision will be blurred for approximately 2 hours (due to the use of mydriatic eye drops) following the eye-testing procedures,

Detailed instructions for the ophthalmological assessments will be provided in the Study Operations Manual/SOPs.

9.3.3.8 Standard 12-lead ECG

A complete standard 12-lead ECG will be recorded in the supine position using a computerised ECG device at the time-points specified in the Schedule of Events (see **Appendix 1** and **Appendix 2**).

The following parameters will be calculated:

- heart rate,
- PR interval,
- QRS-interval,
- QT/ QTcF interval (uncorrected and corrected QT interval according to Fridericia's formulae).

All ECGs recorded will be read by a physician experienced in evaluating ECGs, providing an ECG diagnosis and overall assessment, including clinical significance and changes compare to screening. The data from this central reading will be used for the statistical analysis.

Any clinically significant abnormality on ECG will be checked by repeat ECG. Any clinically significant ECG abnormality that is confirmed by repeat ECG will be assessed in accordance with the instructions in Section 9.3.4 and may be considered to be an AE.

The triplicate ECG recordings at Screening for the purposes of assessing eligibility may be repeated only once. Triplicate ECGs will be performed at all time points, except at Day 3 in Part 1 when single ECGs will be performed.

Detailed instructions for recording and handling of the ECGs will be provided in the Study Operations Manual/SOPs.

9.3.3.9 Laboratory Assessments

9.3.3.9.1 Haematology, Biochemistry, Urinalysis and Urine Microscopy

Blood and urine samples will be collected at the time-points specified in the Schedule of Events (see Appendix 1 and Appendix 2) for assessment of haematology, biochemistry, urinalysis by dipstick, and urine microscopy (only in the event of abnormal and clinically significant results with dipstick). For the parameters to be assayed, see Appendix 5.

On days when the IMP is administered, blood samples must be collected prior to administration of the IMP, and as far as possible at the same time each day during the treatment period.

Detailed instructions for blood and urine sample collection will be provided in the Study Operations Manual/SOPs.

9.3.3.9.2 Alcohol Breath Test and Urinary Cannabis Screen

Breath and urine samples will be tested for alcohol concentration and presence of cannabis, respectively, at Screening to ensure compliance with the Inclusion and Exclusion Criteria (see Sections 6.1 and 6.2).

9.3.3.9.3 Pregnancy Tests

A highly sensitive pregnancy test, i.e. beta human chorionic gonadotropin level, and the verification of the date of the last menstrual period will be performed in WOCBP at the time-points specified in the Schedule of Events (see Appendix 1 and Appendix 2).

The test performed at baseline closest to and before the first IMP administration and at the Day 13 visit (at least 24 hours after the last IMP intake) or Early Termination visit if done before Day 13 visit, must be a serum test. In case a repeat test is needed during screening at the site, it can be a urine test providing the initial testing was serum and that the repeat is approved by the sponsor.

Tests at other time points may be urine or serum, however serum is preferred where feasible, i.e. when blood collection for another purpose is already scheduled at that time-point.

Any positive pregnancy test after the first IMP administration up to and including the Day 13 visit or Early Termination Visit, if done before Day 13 visit, must be confirmed by a serum test.

If the menstrual period is delayed, with over one month between menstruations, confirmation of absence of pregnancy with a pregnancy test is mandatory. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.

9.3.3.9.4 Remainder and Exploratory Samples, and Future Use

Where feasible, remainder tissue samples collected from study procedures, e.g. skin, microfilariae and nodules will be retained for possible future research. In addition, specific exploratory samples of plasma and urine will be collected at the time-points specified in the Schedules of Events (see Appendix 1 and Appendix 2).

The samples may be used in the future for research on onchocerciasis and other parasitic diseases, including identification of biomarkers of molecular, immunological or genetic origin to develop diagnostic tools for onchocerciasis and increase the knowledge on the disease and response to the IMPs.

Preparation and storage of the samples will be described in the Study Operations Manual/SOPs. The samples may be stored indefinitely after the end of the study. The coded samples will only be transferred providing the relevant documents (e.g., Materials Transfer Agreement) have been submitted to the regulatory authorities and ethics committee(s) if required.

These samples are optional, and subjects may still participate in this study if they do not consent to the collection of exploratory samples and use of their samples for future scientific studies via the informed consent document. If consent is not given, the remainder samples will be discarded after completion of the study and specific exploratory samples will not be collected. All samples transferred for future research will be anonymised.

9.3.4 Safety - Adverse Event Definitions and reporting

In this section, the term "reporting" refers to data collection on AEs in source documents, as well as to informing the Sponsor via the eCRF. The term "safety reporting" refers to time-limited additional reporting of individual case safety reports (SAE, pregnancy, child) to the Sponsor, and where required to ethics committee(s) and regulatory authorities.

9.3.4.1 Definition of Adverse Event

An adverse event (AE) is defined as:

"Any untoward medical occurrence in a clinical trial subject administered a medicinal product, and which does not necessarily have a causal relationship with that treatment.

It can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product."[78]

The definition of an AE includes worsening in severity or frequency of pre-existing conditions (medical history) before the first IMP administration and abnormalities of procedures (e.g. ECG, x-ray, physical or ophthalmological examination) or laboratory results that are assessed as "clinically significant".

What is not an AE, and not captured on the AE page:

- Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are not considered as AEs;
- Lack of efficacy of the IMP is not considered as AE.

9.3.4.2 Assessment of Abnormalities from Laboratory Tests or Other Procedures

For every laboratory test/procedure, the Investigator will evaluate if the result of the laboratory test/procedure is normal or abnormal. If abnormal (after repeat testing, if indicated), the Investigator will assess whether the finding is "clinically significant" or not. An abnormal result on a laboratory test/procedure must be compared with the previous value taking into account normal values in the studied population/country.

If the result of a laboratory test/procedure is abnormal and the abnormality assessed as clinically significant, it should be reported as an AE.

Abnormalities on laboratory tests/procedures (e.g. ECG) or worsening in severity or frequency of pre-existing abnormalities should be assessed as "clinically significant" and therefore must be reported as AE if they meet at least one of the following conditions:

- The abnormality suggests a disease and/or organ toxicity and this abnormality was not present at the screening visit or is assessed as having progressed since the screening visit;
- The abnormality results in discontinuation of the IMP;
- The abnormality requires medical intervention or concomitant therapy.

When reporting an abnormal result on laboratory test/procedure as an AE, a clinical diagnosis should be recorded rather than the abnormal value itself, if available (e.g. acute pancreatitis instead of each finding separately: high levels of amylase, high levels of lipase, abdominal pain

and vomiting; e.g. “hypokalaemia” rather than “decreased potassium levels”; “anaemia” rather than “decreased red blood cell count).

An event that occurs after signature of the ICF and prior to the first IMP administration is not considered an AE per se but as an “event” that could be due to the disease or specific circumstances in which the subject has been placed (e.g. “protocol related” which may be caused by the participation to the trial).

9.3.4.3 Serious Adverse Event

An AE is defined as serious if it:

- Results in death,

  i.e. causes or contributes to death;
- Is life-threatening,

  In this context refers to an AE in which the subject was at risk of death at the time of the AE; it does not refer to an AE that hypothetically might have caused death if it had been more severe;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,

  i.e. the AE requires at least an overnight admission or prolongs hospitalisation beyond the expected length of stay. Hospital admissions for surgery planned before study entry, for social reasons, for any elective surgery (i.e. plastic surgery), for uncomplicated delivery or per protocol or for normal disease management (including treatment adjustment) are not to be considered as SAE according to this criterion (i.e. if the protocol requires planned hospitalisation);
- Results in persistent or significant disability or incapacity,

  i.e. the AE results in a substantial disruption of the subject’s ability to conduct normal activities;
- Is a congenital anomaly or birth defect,

  i.e. an AE outcome in a child or foetus of a subject exposed to the IMP before conception or during pregnancy;
- Is an important medical event, i.e. is medically significant,

  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events/reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, potential drug induced liver injury, blood dyscrasias or convulsions that do not result in hospitalisation. Any suspected transmission via a medicinal product of an infectious agent is also considered as a serious AE.[78]

For the purposes of the study, stillbirth and spontaneous or induced abortion will also be considered as an SAE.

Although exposure during pregnancy and overdose are not always associated with an AE, these events must be handled as defined in Sections 9.3.4.9 and 9.3.4.11).

For the purpose of this study, prolongation of hospitalisation that is not related to a medical event but related to any social and/or financial reasons or logistical reasons, will not be considered as an SAE.

SAE onset/start date: Start date of SAE or date when the AE becomes serious (see seriousness criteria of an SAE).

SAE end/stop date: SAE end date is the date of AE recovery.

9.3.4.4 Eliciting Adverse Event Information

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

In addition, to avoid bias in eliciting AEs, subjects will be questioned about the occurrence of AEs at the time-points indicated in the Schedules of Events (see Appendix 1. and Appendix 2. Schedule of Events in Part 2), with general non-leading questions such as "Since xxx (e.g. last visit) have you had any health problem?" or "How are you feeling?".

All AEs (serious and non-serious) must be recorded on the source documents and AE pages of the eCRF regardless of the assumption of a causal relationship with the IMP. The definition, reporting, and recording requirements for AEs are described in Section 9.3.4.

Information on AEs must be evaluated by a physician.

Each AE is to be classified by the Investigator as serious or non-serious (see definition of a SAE in Section 9.3.4.3). This classification will determine the reporting procedure for the event.

In addition, the frequency, seriousness, severity (see Section 9.3.4.6) and causality (see Section 9.3.4.7) assessment of AEs will be described.

Non-serious AEs are to be recorded in the eCRF, including description of the event, onset date, end date, severity, seriousness, relationship to all study drugs, actions taken and outcome. Start and stop times are to be recorded when available during the in-house period in order to capture Treatment Emergent Adverse Event (TEAE).

Only one AE and the maximum severity will be recorded in the eCRF for each separate event. If the AE resolves but then recurs, each will be recorded as a separate AE, with the appropriate start and stop times.

SAEs will be reported both on the AE page of the eCRF and the SAE forms.

9.3.4.5 Adverse Event Reporting Period

In this protocol, the reporting period is different for AEs and for SAEs:

- Non-serious AEs: all non-serious AEs will be reported from administration of the first intake of IMP until the subject's end of study participation (see Section 3.4).
  Furthermore, non-serious events that occur in the screening period (from signature of the ICF) until before the first intake of the IMP and that are judged as related to study participation (e.g. haematoma due to venipuncture, wound infection due to skin snips), will be recorded on the AE page of the eCRF.
- SAEs: all SAEs must be reported after signature of the ICF during the screening period until the subject's end of study participation (as defined in Section 3.4) on the AE page of the eCRF and the SAE form.

All treatment emergent AEs that occur during the AE reporting period as defined in this section must be reported, whether or not the event is considered treatment related.

In addition, any SAE that occurs after the end of the AE reporting period and that the Investigator assesses as possibly, probably or definitely related to the IMP or to participation in the study may also be reported as an SAE.

Screening failure: beyond the date of screening failure (to be recorded), only serious study-related events will be reported.

9.3.4.6 Grading of Adverse Event Severity

For each serious and non-serious AE, the Investigator is required to assess the severity of each AE.

It is to be noted the distinction between severity and seriousness of AEs. A severe AE is not necessarily a SAE.

The severity for an AE should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (see Appendix 6), as a guide in the grading of the severity of AEs. Certain grading definitions have been adapted to ensure they are appropriate for the IMP, the disease and patient population.

The exceptions are:

- The Vaccine Trial Grading Scale 2007, from the U.S. FDA Center for Biologics Evaluation and Research,[79] will be used for:
  - haemoglobin
  - eosinophils
  - blood urea nitrogen
  - total protein
  - urine glucose

- For values in the urinalysis with no grading available in either CTCAE version 5.0 or Vaccine Trial Grading 2007, the Investigator will use the terminology mild, moderate, severe, life-threatening or death described below.
- In case of AEs that are not described in the CTCAE version 5.0 AE severity grading system, nor in the exceptions listed above the Investigator will use the terminology mild, moderate, severe, life-threatening or death to describe the maximum severity of the AE as follows:
  - Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated, (e.g. no reduction in daily activities is required);
  - Moderate: The subject experiences sufficient discomfort to interfere with or reduces his or her usual level of activity;
  - Severe: Significant impairment of functioning: the subject is unable to carry out usual activities and/or the subject's life is at risk from the event.
  - Life-Threatening: The subject is at significant risk of life; it does not refer to an event which hypothetically might have caused death if it were more severe (life-threatening consequences, urgent intervention required).
  - Death: Death related to an event.

This information will be entered on the AE page of the eCRF.

When the severity of an AE changes over time, each change in severity will be recorded in the source documents until the event resolves. However, only one AE and the maximum severity will be recorded in the eCRF for each separate event. If the AE resolves but then recurs, each recurrence will be recorded as a separate AE, with the appropriate start and stop times.

9.3.4.7 Adverse Event Causality Assessment

For each serious and non-serious AEs, the Investigator is required to assess the possible relationship between the AE and each IMP, i.e. to determine whether there exists a reasonable possibility that the IMP(s) caused or contributed to the AE(s).

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

- Definitely related. The AE and administration of IMP are related in time, and a direct association can be demonstrated;
- Probably related. The AE and administration of IMP are reasonably related in time, and the AE is more likely explained by the IMP than other causes;
- Possibly related. The AE and administration of IMP are reasonably related in time, and the AE can be explained equally well by causes other than the IMP;
- Probably not related. A potential relationship between IMP and the AE could exist (i.e. the possibility cannot be excluded), but the AE is most likely explained by causes other than the IMP;
- Not related. The AE is clearly explained by another cause not related to the IMP.

Note: for regulatory reporting purposes, when compared to binary classification, “not related” corresponds to “not related” and “probably not related” and “related” corresponds to “possibly”, “probably”, and “definitely related”.

To help the Investigator with the decision binary tree (related/not related) in the evaluation of causality, the Council for International Organisations of Medical Sciences VI group recommends that the Investigator should consider the following before reaching a decision:

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

In addition, for SAEs, the Sponsor will also perform a causality assessment in accordance with Sponsor’s standard operating procedures.

9.3.4.8 Safety Reporting Requirements

Each AE is to be classified by the Investigator as serious or non-serious. This classification will determine the reporting procedure for the event.

All SAEs are to be reported immediately (within 24 hours of awareness of the SAE by the Investigator), to SAETYL01study@dndi.org, using the SAE report form. This includes a

description of the event, onset date and type, duration, severity, relationship to each of the IMPs, outcome, measures taken and all other relevant clinical and laboratory data.

The initial report is to be followed by submission of additional information (follow-up SAE form) as it becomes available. Any follow-up reports should be submitted as soon as possible, and if possible within 5 working days from awareness of the information by the Investigator.

SAEs should also be reported on the AE page of the eCRF. It should be noted that the form for reporting of SAE (SAE form) is not the same as the AE section of the eCRF. Where the same data are collected, the two forms must be completed in a consistent manner, and the same medical terminology should be used.

In addition to immediately reporting SAEs to DNDi, the Investigator will immediately notify the regulatory authorities and ethics committee(s) of SAEs (and non-serious AE if required by the local regulatory requirements), and follow-up information, that occur during this trial, if applicable, in accordance with the standard operating procedures/guidelines/regulations issued by the regulatory authorities and ethics committee(s).

A suspected unexpected serious adverse reaction (SUSAR) is a suspected AE related to an investigational medicinal product that is both unexpected and serious.

DNDi, the Sponsor is responsible for determining the expectedness of the event for each IMP, using the reference safety information defined for the study, contained in the Investigator Brochure for ABBV-4083, and in the Prescribing Information for albendazole and ivermectin.[57,63,65]

DNDi will notify the regulatory authorities and ethics committee(s) of all SUSARs (if applicable based on local requirements) in compliance with local safety reporting requirements.

If unblinding is required for expedited reporting (as per local requirements), reporting of SUSARs to the regulatory authorities and ethics committee(s) will not involve any personnel at the investigational centre or other members of the Sponsor's study team, to preserve the study blind.

9.3.4.9 Exposure in utero

If a trial subject becomes or is found to be pregnant (based on date start last menstruation period) while receiving any IMP or within 1 month of discontinuing the IMP, the Investigator must submit the event on a "Pregnancy Surveillance Form" in accordance with the same process and timelines as defined for SAEs (see Section 9.3.4.8).

This must be done irrespective of whether an AE has occurred. The information submitted should include the start date of last menstruation period (or the best estimation) and the anticipated date of delivery.

The Investigator will follow the subject until completion of the pregnancy or until pregnancy termination (i.e. induced / spontaneous abortion). The Investigator will provide pregnancy follow-up or outcome information on a "Pregnancy Surveillance Form".

In the case of a live birth, a medically qualified person (preferably a paediatrician) should assess the infant at the time of birth and submit a "Child Surveillance Form". The Investigator will offer the parents follow-up on infants exposed to the study treatment in utero until they reach 24 months of age.

A pregnancy is not a SAE. Any unfavourable outcome meeting at least one seriousness criteria i.e. in the case of unfavourable pregnancy outcome (spontaneous and induced abortion, still

birth) or congenital abnormality shall be reported using the "SAE form" (in addition to the Pregnancy/Child Surveillance Form).

9.3.4.10 Adverse Event Follow-up

All AEs should be followed until:

- they are resolved; or
- the Investigator assesses them as "chronic" or "stable"; or
- the subject's participation in the trial ends, i.e. as defined in Section 3.4.

The Principal Investigator or Co-investigator may or will interrupt or suspend treatment due to serious safety issues in order to protect the subjects. In addition, all SAEs, whether related or not, must continue to be followed even after the subject's end of study participation in order to collect the outcome. Such events should be followed until they resolve or until the Investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the AE page of the eCRF (up to the end of study participation) and SAE form (up to and after the end of study participation).

For SAEs that occur after the subject's end of study participation, see Section 9.3.4.8.

9.3.4.11 Overdose

All overdoses with the study treatment will be recorded in the eCRF. If the overdose is symptomatic and clinically significant, it will also be reported as an AE.

In the event of an overdose with the study treatment, symptomatic and supportive therapy should be given as appropriate, and the Investigator should contact the Sponsor's Medically Responsible Person.

Medication errors with the study treatment committed by study personnel that result in a possible overdose, as well as all medication errors, must be documented as protocol deviations and reported to the Sponsor and the regulatory authorities and ethics committee(s) if required in accordance with the requirements of the local ethics committee(s) and regulatory authorities.

9.3.4.12 Monitoring of AEs Outside the Investigational Centre

To ensure appropriate and timely management of AEs, a process will be set up for reporting and communication of any AEs that occur when the subject is not at the investigational centre. The process will be described in the Study Operations Manual/SOPs.

10 Statistical Analyses

10.1 Statistical Hypotheses

10.1.1 Primary Hypothesis in Part 1

The primary hypothesis for the proof of concept in Part 1 is that more worms will have *Wolbachia* depletion at 6 months in the subjects who completed treatment with ABBV-4083 for 7 days (Arm A), ABBV-4083 for 14 days (Arm B), ABBV-4083 + albendazole for 7 days (Arm C), or ABBV-4083 for 7 days + albendazole for 3 days (Arm D) than in subjects treated

with albendazole for 7 days (Arm E) among all subjects who completed treatment and who had live female worms from nodulectomies at 6 months.

The primary hypothesis to satisfy the combination rule in Part 1 is that more worms will have *Wolbachia* depletion at 6 months in the subjects treated with ABBV-4083 + albendazole for 7 days (Arm C) than in subjects treated with albendazole for 7 days (Arm E) or those treated with ABBV-4083 for 7 days (Arm A) among all subjects who completed treatment and had live female worms from nodulectomies at 6 months. If the combination arm of ABBV-4083 for 7 days + albendazole for 3 days (Arm D) is to advance to Part 2 and ABBV-4038 for 7 days + albendazole for 7 days (Arm C) is not, then the combination rule will be tested for ABBV-4083 for 7 days + albendazole for 3 days (Arm D) in Part 1. Of note, the possible substitution of ABBV-4083 for 7 days plus albendazole for 3 days in place of ABBV-4038 + albendazole for 7 days will not be continuously noted below for brevity sake.

10.1.2 Primary Hypotheses in Part 2

The primary hypothesis for Part 2 is that more subjects treated with one or more of the active regimens selected from Part 1 (Arms K, L and M) will be without skin microfilariae at 24 months as compared to subjects treated with placebo (Arm N1, base scenario) or ABBV-4083 for 7 days (Arm N2, alternate scenario).

Combination Rule Hypothesis for Part 2 Alternative Scenario

If the primary hypothesis to satisfy the combination rule in Part 1 is not satisfied and ABBV-4083 + albendazole for 7 days (Arm C in Part 1) is to be carried forward to Part 2 (as either Arm K with ivermectin and Arm L without ivermectin, or as Arm M with or without ivermectin), an additional hypothesis using appropriate subjects from both Part 1 and Part 2 will be that more worms will have *Wolbachia* depletion at 6 months in subjects treated with ABBV-4083 + albendazole for 7 days (Arm C for Part 1 and Arm K plus Arm L [or alternately Arm M if appropriate] for Part 2) than in subjects treated with ABBV-4083 for 7 days (Arm A for Part 1 and Arm N2 for Part 2) among all subjects who completed treatment and who had live female worms from nodulectomies at 6 months.

In the case that ABBV-4083 for 7 days + albendazole for 3 days (Arm D in Part 1) is selected for Part 2 and ABBV-4083 + albendazole for 7 days (Arm C in Part 1) is not selected, and the primary hypotheses for satisfying the combination rule in Part 1 are not satisfied, then the arm or arms containing ABBV-4083 for 7 days + albendazole for 3 days will be treated as described elsewhere in this document for ABBV-4083 + albendazole for 7 days in the Alternate Scenario, and the data combined with Arm D in Part 1 for analysis.

10.1.3 Key Secondary Hypotheses in Part 2

The key secondary hypotheses in Part 2 are as follows:

- The first secondary hypotheses for Part 2 (Endpoint 2a) are that a smaller mean percentage of female adult worms per subject will be alive at 24 months among the subjects who completed treatment with one or more of three assigned regimens selected from Part 1 (Arms K, L and M) compared to either placebo (Arm N1) or ABBV-4083 for 7 days (Arm N2).
- The second secondary hypotheses for Part 2 (Endpoint 2b) are that a larger mean percentage of live female adult worms will have only degenerated embryos in their uteri

per subject at 24 months among the subjects who completed treatment with one or more of three regimens selected from Part 1 (Arms K, L and M) compared to either placebo (Arm N1) or ABBV-4083 for 7 days (Arm N2).

10.2 Analysis Sets

The analysis sets are:

- Intention-to-treat (ITT) population: all randomised subjects who received at least one dose of IMP.
- Primary population for Part 1 primary endpoint and Part 2 combination rule endpoint for Alternative Scenario: Per protocol (PP) for nodulectomy at 6 months (ND6M), i.e. all ITT subjects who had Month 6 nodulectomy with live female adult worms, who completed treatment and who did not take prohibited medication during the study (see Appendix 8 - Sections II and IV).
- Primary population for Part 2 proportion of subjects with microfilaria depletion at Month 24 endpoint: PP population for microfilaria, defined as all subjects in the ITT population who had microfilaria-positive skin-snips at baseline, who completed treatment, had skin snips at Month 24 or received ivermectin rescue before Month 24, and who did not take prohibited medication during the study (see Appendix 8 - Sections II and IV).
- Primary population for Part 2 secondary endpoints 2a: PP population for nodulectomy at 24 months (ND24M), i.e. all ITT subjects who had Month 24 nodulectomy with female adult worms, who completed treatment and who did not take prohibited medication during the study.
- Primary population for Part 2 secondary endpoints 2b: PP population for nodulectomy at 24 months (ND24M) with live female adult worms, i.e. all ITT subjects who had Month 24 nodulectomy with live female adult worms, who completed treatment and who did not take prohibited medication during the study.
- Safety population: all randomised subjects who received at least one dose of IMP.

Subjects who take prohibited medications that may have an impact on the study objectives (Appendix 8- sections II and IV) are excluded from the PP populations. Specifically subjects who take medications with an anti-filarial or anti-Wolbachia effect at any time during the study (Appendix 8-section II) or strong CYP3A inducers or dexamethasone during the treatment period that may lower ABBV-4083 or albendazole exposures (see Appendix 8 - Section IV) are excluded from the PP population.

Completed treatment for Part 1 is defined as taking at least 6 out of 7 days of randomised ABBV-4083, ABBV-4083 + albendazole or albendazole alone (Arms A, C or E, respectively), 12 out of 14 days of randomised ABBV-4083 (Arm B) or 6 out of 7 days of randomised ABBV-4083 and all of 3 days of randomised albendazole (Arm D). The same definitions of treatment completion will be applied to the similar arms in Part 2, except that subjects must also be administered ivermectin or matching placebo at Month 6 to be considered as having completed treatment.

10.3 Determination of Sample Size

10.3.1 Determination of Sample Size in Part 1

For the Part 1 primary hypothesis that compares the proportion of live female adult worms without *Wolbachia* at Month 6 between a single-drug ABBV-4083 arm (Arm A or Arm B) and the albendazole arm (Arm E), an alternating logistic regression will be used to compare the endpoint between two arms, taking into account the clustering of this worm-level endpoint by subject. Using simulations that add substantial clustering by subject to the endpoint values and assuming the number of worms in each subject varies from 1 to 10,[54] following the multinomial distribution with probability = (0.20, 0.16, 0.16, 0.16, 0.08, 0.08, 0.08, 0.03, 0.03, 0.02) for values (1, 2, 3, 4, 5, 6, 7, 8, 9, 10), 17 subjects per arm will provide 88% power to detect the difference between a single-drug ABBV-4083 arm (Arm A or Arm B) where 70% of worms are without *Wolbachia* and the albendazole arm (Arm E) where 30% of worms are without *Wolbachia* (2-sided α =0.10). The clustering of the endpoint values by subject is provided by the Pearson intraclass correlation coefficient (ICC) for binary outcomes[80] and was given as ICC = 0.54 for simulated arms where 70% or 30% of the worms are without *Wolbachia*.

For the Part 1 primary hypothesis that compares the proportion of live female adult worms without *Wolbachia* at Month 6 between the combination arm of ABBV-4083 + albendazole for 7 days (Arm C) and the single-drug ABBV-4083 arm (Arm A), 25 subjects per arm will provide 81% power to detect the difference between the combination arm where 90% of worms are without *Wolbachia* and the single-drug arm where 70% of worms are without *Wolbachia* (2-sided α =0.10 using alternating logistic regression). ICC = 0.54 was added to the simulated arm where 70% of the worms are without *Wolbachia*. Minimal clustering (ICC = 0.01) was added to the simulated arm where 90% of the worms are without *Wolbachia* because the difference between subjects would be negligible for such a high response rate. 30 subjects will be enrolled per arm to account for 17% drop out by Month 6.

10.3.2 Determination of Sample Size in Part 2

For the Part 2 primary hypothesis in the Base Scenario that compares the proportion of subjects without skin microfilariae at Month 24 between an active arm (Arm K, L or M) and the placebo arm (Arm N1), 62 subjects in the active arm and 31 subjects in the placebo arm will provide 91% power to detect the difference between an active arm (Arm K, L or M) where 70% of subjects are without skin microfilariae at Month 24 and the placebo arm (Arm N1) where 30% of subjects are without microfilariae at Month 24, using a logistic regression with 2-sided α=0.017. In addition, 62 subjects per arm will provide 80% power to detect the difference between two active arms where 90% and 70% of subjects are without skin microfilariae at Month 24, respectively, using a logistic regression with nominal 2-sided α=0.05. Assuming a 25% drop-out rate by Month 24, 84 subjects in each active arm and 42 subjects in the placebo arm are planned to be enrolled.

For the Part 2 primary hypothesis in the Alternate Scenario that compares the proportion of subjects without skin microfilariae at Month 24 between each active arm (Arm K, L or M) and the control arm (Arm N2: 7 days of ABBV-4083), 62 subjects per arm will provide 84% power to detect the difference between an active arm (Arm K, L or M) where 90% of subjects are without skin microfilariae at Month 24 and the control arm (Arm N2) where 65% of subjects are without microfilariae at Month 24 , using a logistic regression with 2-sided α=0.017.

For the Part 2 combination rule hypothesis in the Alternate Scenario that compares the proportion of live female adult worms without *Wolbachia* at Month 6 between the combination arms of ABBV-4083 + albendazole for 7 days (Arm K plus Arm L) and the ABBV-4083 single drug arm (Arm N2), 17 subjects per each of Arms K and L for a total of 34 subjects in Part 2 in addition to the 25 subjects per arm in Part 1 will be able to provide an overall power of 96% to detect the difference between the combination arm where 90% of worms are without *Wolbachia* and the single drug arm where 70% of worms are without *Wolbachia* (2-sided α =0.10) in either Part 1 or Part 2, using an inverse normal combination test that combines the p-values of alternating logistic regressions that use data from Part 1 only and Part 2 only. The assumption for the number of worms in each subject in Part 2 is adjusted to a multinomial distribution with probability = (0.22, 0.18, 0.17, 0.16, 0.08, 0.06, 0.06, 0.03, 0.02, 0.02) for values (1, 2, 3, 4, 5, 6, 7, 8, 9, 10) in order to account for the design that only worms from one nodule per subject in Part 2 will be used for this analysis. If Part 1 Arm B of ABBV-4083 for 14 days is used for Arms K and L of Part 2, Arm M would be the 4083/albendazole combination that is compared to Arm N2. 17 subjects in Arm M Part 2 in addition to the 25 subjects per arm in Part 1 will be able to provide an overall power of 95% using the same method. Assuming 17% of the subjects per arm drop out by Month 6, the enrolment in the alternate scenario will require at least 25% of subjects of those retained to Month 6 nodulectomy to have > 1 nodule site in the arms used to test this hypothesis to obtain the power shown above.

10.4 Handling of Potential Intercurrent Events for the Primary and Key Secondary Endpoints

Subjects who do not complete the treatment as defined above will be excluded from the PP populations (but will be included in the ITT analyses). Subjects in Part 2 with evidence of reinfection will be included in all analyses as it is not possible to distinguish between reinfection and a failure in this study. However, in sensitivity analyses, those subjects will be excluded from efficacy analysis. Subjects in Part 2 who do not have skin snips at Month 24 will be excluded from the PP for microfilaria population, except those who received ivermectin rescue before Month 24. Any subject who received ivermectin rescue before Month 24 as allowed per protocol will be counted as a failure in both the PP and ITT analyses of the Part 2 primary and key secondary endpoints. Subjects who do not have nodulectomy data at Month 6 (for Part 1 and for Part 2 Alternate Scenario) or Month 24 (for Part 2) will be excluded from the PP for the ND6M or ND24M populations, respectively. Subjects who take prohibited medications (see Appendix 8-sections II and IV) will be excluded from the PP analyses; subjects who take medications with an anti-filarial or anti-Wolbachia effect at any time during the study (see Appendix 8 - Section II) will be counted as failures in the ITT analyses.

In the ITT analysis of the primary and key secondary endpoints, if the result is missing for the assessment, the assessment of that outcome will be a failure if the absence of data is due to administration of prohibited medication or withdrawal due to efficacy or safety issue. In the event of withdrawal of informed consent, subject lost to follow-up or withdrawal for a reason independent from the treatment (e.g. moving, lethal accident), multiple imputation will be used to impute the missing data.

10.5 Population Level Summary and Analysis for the Primary Endpoints

The Part 1 primary and combination endpoints, the proportion of adult female worms without *Wolbachia* endobacteria assessed by immunohistology at 6 months, will be summarised among

the PP for ND6M population, and the odds ratio for each of the treatment arm comparisons of interest (Arm A vs E and Arm B vs E; Arm C vs E, Arm C vs A; Arm D vs E, Arm D vs A) will be calculated using contrasts within an alternating logistic regression model with treatment arm as factor and also accounting for within-subject correlation, each at 2-sided $\alpha = 0.10$.

The Part 2 primary endpoint of the percentage of subjects without skin microfilariae at Month 24 will be summarised across the PP for microfilariae population, and the adjusted odds ratio for each of the 3 active treatment arms will be compared to the comparator arm (Arm K vs N1 or N2, Arm L vs N1 or N2, and Arm M vs N1 or N2) using contrasts within a logistic regression model with treatment arm as factor and number of sites per subject (1, > 1) and mean baseline mf (≤ 5, > 5) as covariates at 2-sided $\alpha = 0.017$. Supportive subgroup analyses for the primary endpoint will also be performed for at least the following subgroups: number of sites per subject (1, > 1) and mean baseline mf (≤ 5, > 5).

The Part 2 combination rule endpoint for the alternate scenario, the proportion of adult female worms without *Wolbachia* endobacteria assessed by immunohistology at 6 months across all subjects treated with the same regimens in Parts 1 and 2 will be summarised among the PP for ND6M population, and the odds ratio for the comparison of interest (Arm K plus Arm L vs N2 [or Arm M vs Arm N2 if ABBV-4083 for 14 days is chosen for Arms K and L]) will be calculated using contrasts within an alternating logistic regression model with treatment arm as factor. P-values for the odds ratio of Part 1 and Part 2 will be combined using an inverse normal combination test and tested at 2-sided $\alpha = 0.10$.

10.6 Population Level Summary and Analysis for the Key Secondary Endpoints

The Part 2 secondary endpoint 2a, the mean percentage of live female adult worms per subject as assessed by histological examination of nodules collected during nodulectomy at 24 months, will be summarised among the PP for ND24M population and the mean difference between each of the 3 active treatment arms and the comparator arm (Arm K vs N1 or N2, Arm L vs N1 or N2, and Arm M vs N1 or N2) will be calculated using a stratified Mann-Whitney U test with number of sites per subject (1, > 1) and mean baseline mf (≤ 5, > 5) as strata, with α allotted according to the graphical approach in Figure 2. In the exploratory regimen/duration ranging, the percentage of live adult female worms per subject at Month 24 will be similarly compared between the 3 active arms, each at nominal 2-sided $\alpha = 0.05$.

The Part 2 secondary endpoint 2b, the mean percentage of live female adult worms with degenerated embryos in uterus per subject as assessed by histological examination of nodules collected during nodulectomy at 24 months will be summarised among the PP for ND24M with life female adult worms and the mean difference between each of the 3 active treatment arms compared to placebo (Arm K vs N1 or N2, Arm L vs N1 or N2, and Arm M vs N1 or N2) will be calculated using a stratified Mann-Whitney U test with number of sites per subject (1, > 1) and mean baseline mf (≤ 5, > 5) as strata, with α allotted according to the graphical approach in Figure 2. In the exploratory regimen/duration ranging, the mean percentage of adult female worms with degenerated embryos per subject and per nodule will be similarly compared between the 3 active arms, each at nominal 2-sided $\alpha = 0.05$.

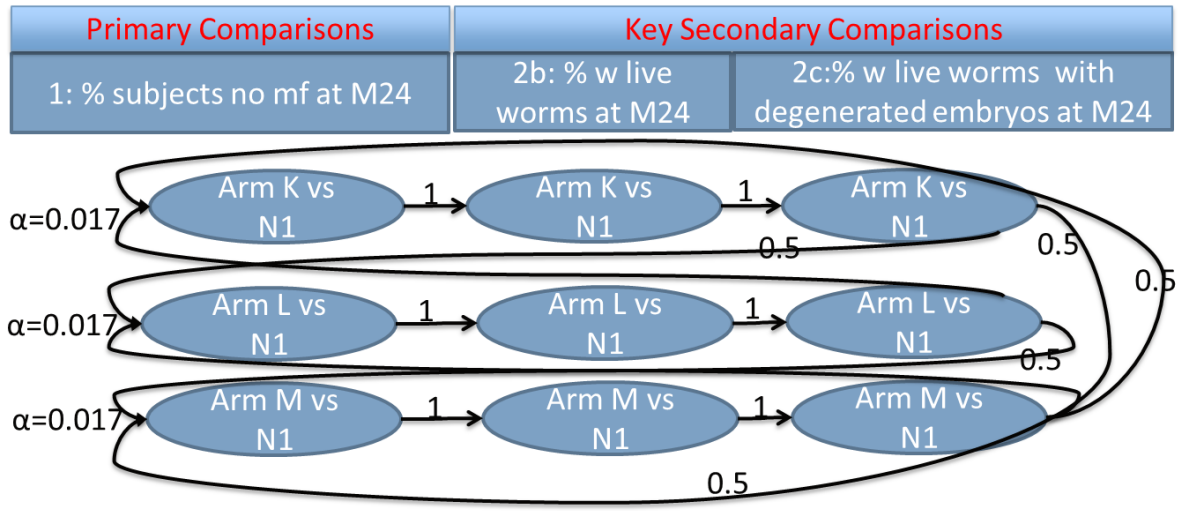
The primary and key secondary endpoints will also be analysed on the ITT population.

10.7 Multiplicity Adjustment

Since Part 1 is a Phase-II proof-of-concept study, no adjustment will be made for the multiple comparisons in the primary endpoint (Arm A vs Arm E, Arm B vs Arm E, Arm C vs Arm A, Arm C vs Arm E, Arm D vs Arm A and Arm D vs Arm E). Each comparison will be controlled at 2-sided $\alpha = 0.10$.

In Part 2, the multiplicity adjustment to control the overall Type I error rate at 5% will include: (1) Bonferroni allocation of $\alpha = 0.017$ to each primary endpoint comparison: Arm K vs Arm N1, Arm L vs Arm N1, and Arm M vs N1; (2) a graphical approach to multiplicity adjustment to control the family-wise error at 0.05 (see Figure 6). The same method will be used in the Part 2 Alternate Scenario, with comparisons between Arms K-M and Arm N2.

Figure 6. Graphical Approach to Multiplicity Control in Part 2



Of note, the parallel graphical approach above shows how the α is passed to the next comparison if the null hypothesis is rejected.[81]

In the Alternate Scenario of Part 2, the primary endpoint for satisfying the combination rule in Part 1 continued in Part 2 (combination rule endpoint) is conducted at 2-sided $\alpha = 0.10$ with no need to adjust for multiplicity per Section 5.5.2 of the European Medicines Agency Guideline on Multiplicity Issues for Clinical Trials.[82]

10.8 Statistical Analysis of Safety

All safety analyses will be performed on the Safety Population, which consists of all subjects who received at least one dose of IMP. Safety will be assessed by AEs, laboratory tests, vital signs, and ECG variables. Details of the analyses will be provided in the Statistical Analysis Plan.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an AE with an onset date that is after the first intake of IMP and no more than 30 days after the last intake of IMP. The number and percentage of subjects experiencing TEAEs will be tabulated using MedDRA system-organ class and preferred term, as well as by severity and by relationship to the IMP as assessed by the Investigator. Summaries of SAEs, deaths, AEs leading to discontinuation will also be provided.

For laboratory test and vital signs variables, mean change from baseline and percentage of subjects with on-treatment laboratory values of CTCAE 5.0 adapted scale grade 3 or 4 will be summarised.

10.9 Interim Analysis of Part 1 and DSMB Recommendation to Proceed to Part 2

Once subjects in Part 1 have completed or prematurely discontinued the study, up to and including nodulectomy at 6 months, a database lock for Part 1 database and an interim analysis of data from Part 1 will be conducted by the Sponsor and the randomisation code unblinded. The unblinded data will be reviewed by the Sponsor and the DSMB (see Section 13.3), for futility and risk/benefit ratio. Taking into account the recommendations of the DSMB, especially regarding the safety assessment of the data, the Sponsor will decide whether or not to proceed to Part 2, and with which dose regimens.

Selection of up to two acceptable/suitable doses / regimens for Part 2 will be based on analysis of all of available unblinded data from Part 1, including safety and tolerability of ABBV-4083 and ABBV-4083 + albendazole, *Wolbachia* depletion, disruption of embryogenesis and an exploratory surrogate marker, microfilaria *Wolbachia*, observed at Months 3 and 6.

10.10 Interim Analysis of Part 2 and DSMB Recommendation for Phase III

After all subjects in Part 2 have performed the Month 18 visit or prematurely discontinued from the study, the safety and skin microfilaria data through Month 18 will be analysed by an independent unblinded statistician (not associated with the study team) for review by the DSMB. The study team, sponsor and patients will remain blinded to the randomization and results. Details of the analyses and methods of maintaining the blind will be described in a separate statistical analysis plan. Based on this analysis, the DSMB may recommend a regimen(s) for advancement into a subsequent Phase-III study in advance of the primary endpoint at Month 24. The recommendation will be based on safety, tolerability and efficacy within target limits provided by the Sponsor. If no recommendation is feasible based on data through Month 18, the DSMB will make a recommendation after Month 24 based on all unblinded study results including the Month 24 endpoints.

11 Data Handling and Quality Assurance

11.1 Data Collection

11.1.1 Investigator Site File

The Principal Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These records include the Investigator Site File, subject clinical source documents and the eCRF. The Investigator Site File will contain the logs of subjects screened and randomised, protocol/protocol amendments, SAE Reporting Forms and query forms, approval from ethics committee(s) and regulatory authorities with correspondence, sample of the approved study information document and ICF, completed ICFs, drug accountability records, staff curriculum vitae, training and authorisation forms, hard copies of eCRFs and queries (if applicable), records of maintenance and/or calibration of equipment, and other appropriate documents/correspondence etc. The Principal Investigator is responsible for storing the

Investigator's Site File and other study documentation in a secure location and to archive them at the end of the clinical study.

11.1.2 Case Report Forms

After informed consent, data will be recorded in the source documents (see Section 11.1.3). The study eCRF will be filled out by authorised personnel at the investigational centre. The data include any updates or corrections to SAE Reporting Forms or Pregnancy or Child Surveillance Forms or data clarification forms (DCF) sent to the Sponsor's pharmacovigilance team. Data entry in the eCRF will be supervised, and the eCRFs will be signed electronically by the Principal Investigator.

Study-specific information will be entered into the eCRF/SAE forms/pregnancy or child surveillance forms according to the instructions for eCRF completion provided by the Sponsor. A master subject log containing identifying information (name, etc.) of all subjects screened for the study, together with their screening numbers, will be stored securely by the Investigator. A log will also be kept of all subjects randomised in the study. All eCRF data must be coded, i.e. identified by screening/randomisation number only.

The Investigator will ensure the accuracy, completeness, legibility, and timeliness of all data reported to the Sponsor in the eCRFs/SAE forms/pregnancy or child surveillance forms/DCF and any other additional information that is required. The Investigator is responsible for keeping all consent forms, screening forms, eCRF/SAE forms/pregnancy or child surveillance forms/DCF and the completed master subject log in a secure location.

At the end of the study, a copy of the data from the eCRF will be provided to investigator in an appropriate format, e.g. DVD or flash drive, for long-term archiving.

11.1.3 Source Documents

Source documents may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, and logs of subjects screened/randomised.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

The Investigator must maintain source documents for possible review and/or audit by the Sponsor and/or regulatory authorities. The Investigator or designee will record the date of each subject's visit together with a summary of their status and progress in the study.

11.1.4 Data from Screening Failures

Data on screening failures will be recorded in the Screening Log, source documents and eCRF, for entry in the clinical database. Instructions will be provided in the Study Operations Manual.

For screening failures with an SAE, an SAE Form will also be completed.

11.2 Study Monitoring

Study monitors will review on an ongoing basis the quality and the plausibility of the eCRF data. The monitors will perform regular monitoring – including both remote monitoring, and visits to the investigational centre to verify that the clinical study is conducted in accordance

with the study protocol, ICH GCP E6 and ALCOA guidelines, as well as local GCP guidelines and regulatory requirements.

Monitoring will include checks that the data are authentic and accurate, by verifying eCRFs and study documents (including SAE/pregnancy or child surveillance forms /query forms) versus source documents, by direct inspection, and checking for consistency between them all. The frequency of the monitoring and data checks will be decided and adapted by the Sponsor and defined in the Monitoring Plan.

Prior to the start of the study, the monitors will review with the study personnel the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The monitors will monitor the activity of the investigational centre to ensure that:

- Data are authentic, accurate and complete. Supporting data may be requested, e.g. blood glucose readings to support a diagnosis of diabetes;
- The safety and rights of subjects are being protected;
- The study is being conducted in accordance with the currently approved protocol, including use of the IMP in accordance with the protocol;
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The Investigator and the head of the medical institution, if applicable, agrees to allow the monitors direct access to all study-related documents.

11.3 Data Processing

Processing of study data will be performed in accordance with applicable Sponsor's standards and data cleaning procedures and study Data Management Plan, using a validated database. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. pharmacokinetic laboratory).

For data coding (e.g. AEs, medical history, medication), internationally recognised and accepted dictionaries will be used (e.g. MedDRA and WHODrug Global dictionary). This will be detailed in the Data Management Plan.

11.4 Missing Data

Methods for handling missing data are described in Section 10.4. In addition, any deviation(s) from the original statistical analysis plan will be described in the final clinical study report.

11.5 Audit and Inspection

To ensure compliance with ICH GCP E6 and local GCP requirements if applicable, a member of the Sponsor's quality assurance team, or a designated clinical research organisation, may arrange to perform an audit to assess the conduct of the study at the investigational centre and the handling of the study documents originating there. The Investigator/institution will be informed of the audit findings.

In addition, inspections by regulatory authority and ethic committee representatives are possible. The Investigator should notify the Sponsor immediately of any such inspection.

The Investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to

discuss findings and any issues. Audits and inspections may occur at any time before, during or after completion of the study.

11.6 Archiving of Essential Study Documents

Essential study documents will be archived safely and securely in such a way that ensures that they are readily available upon request from the regulatory authorities.

The essential documents, including Investigator Site File, subject files and source documents will be archived according to local regulations and in accordance with the maximum period of time permitted by the investigational centre. Where the archiving procedures do not meet the minimum timelines required by the Sponsor, i.e. 25 years, alternative arrangements must be made to ensure the availability of the essential documents for the required period.

The Investigator/institution will notify the Sponsor of any change in the arrangements for archiving, e.g. relocation or transfer of ownership.

The essential documents are not to be destroyed without the Sponsor's approval.

12 Premature Study Termination

Both the Sponsor and the Investigator reserve the right to terminate the study at any time prior to inclusion of the intended number of subjects, however they intend to exercise this right only for valid scientific or administrative reasons. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given to the protection of the subjects' safety and well-being.

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

- Insufficient rate of subject inclusions;
- Protocol violations;
- Inaccurate or incomplete data;
- Unsafe or unethical practices;
- Questionable safety of the IMP;
- Suspected lack of efficacy of the IMP;
- Recommendation from the DSMB, regulatory authorities or ethics committee(s);
- Administrative decision.

Reasons for early termination by the Investigator may include but not be limited to:

- Insufficient time or resources to conduct the study;
- Lack of eligible subjects.

If the study is early terminated either by the Sponsor or by the Investigator, the Investigator is required to:

- Complete all eCRFs to the greatest extent possible;
- Return all IMPs and related study materials to the Sponsor;
- Answer all questions from the Sponsor or its representatives related to data on subjects recruited at the investigational centre prior to study termination;
- Ensure that subjects included in the study who have not yet completed the study are followed up with the necessary medical care;
- Provide the national regulatory authorities and ethics committee(s) and the Sponsor with the reasons for the decision in writing.

13 Ethical and Legal Aspects

13.1 Investigator and Other Study Personnel

All study personnel not specifically referred to in this protocol are identified in a separate list of study personnel. The list will be updated as needed; an abbreviated version with personnel relevant for the centre will be available in the Investigator Site File of the investigational centre.

Whenever the term 'Investigator' is used in the protocol text, it may refer to either the Principal Investigator at the investigational centre, or an appropriately qualified, trained and delegated individual in the investigational centre.

The Principal Investigator must sign the protocol signature page and must receive all required external approvals (e.g. regulatory authorities, ethics committees, Sponsor) before subject recruitment may start at the investigational centre. Likewise, all amendments to the protocol must be signed by the Principal Investigator and must have received all required external approvals before coming into effect at the investigational centre.

13.2 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 Investigators. The exact composition, roles and responsibilities of the SRC will be described in the SRC Charter.

The SRC will review safety results regularly (see Section 3.5.2.2.). If > 10% of subjects in any of the arms meets any of the toxicity criteria the SRC will refer to the DSMB. Throughout the study, the SRC will keep the DSMB fully informed of their decisions, including reports from SRC meetings and may consult the DSMB for recommendations.

13.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be established by the Sponsor in accordance with ICH guidelines for GCP.[83]

The composition, roles and responsibilities of the DSMB will be described in detail in the DSMB charter.

The DSMB may recommend stopping enrolment in the event of a negative safety assessment. The DSMB will be comprised of a minimum of three persons, including at least one medically qualified disease expert, a statistician, and other persons, taking into account any requirements specified by the regulatory authorities.

The DSMB will be informed by the SRC if > 10% of subjects in any of the arms meets any of the toxicity criteria (see Section 3.5.2.2). The DSMB will review the reports and make recommendations regarding halting enrolment into Arms A, B, C or D and opening enrolment in appropriate arms with a lower dose of ABBV-4083.

The DSMB will also review and evaluate, at intervals and as defined in the DSMB charter, the progress, scientific validity and data integrity of the clinical trial, the safety data collected during the trial to recommend to the Sponsor to continue, modify or terminate the trial. The DSMB will assess reports on cumulative data about enrolment, subject discontinuation, subject demographic and safety data, including serious and non-serious AEs and other safety

parameters, cases of exposure during pregnancy and outcomes, PK results, concomitant treatments, as well as ad-hoc requests if deemed necessary by the Sponsor and in line with the DSMB charter.

At the end of Part 1 the database from Part 1 will be locked, the randomisation codes broken, and the efficacy and safety results from that part will be prepared by the Sponsor or designee. The DSMB will review all the results to provide a recommendation whether to proceed or not to Part 2, and which dose regimens to include (see Section 10.10).

After all subjects have reached Month 18 of Part 2 or prematurely discontinued from the study, the Part 2 database will be locked and an interim analysis of Part 2 will be performed. An independent unblinded statistician(s) not associated with the study team will prepare efficacy results based on microfilaria and subject discontinuation, subject demographic and safety results for review by the DSMB. Based on these results the DSMB will make recommendation to an unblinded senior management committee, separate from the study team, to review the interim analysis results and to start Phase III studies. All study team members, patients and investigators will remain blinded until lock of the database at Month 24. Further details on the Part 2 Month 18 interim analysis will be provided in a separate DSMB Charter.

13.4 Funding and Financial Disclosure

13.4.1 Funding of the Study

The study will be funded by the Sponsor.

13.4.2 Financial Disclosure

The Investigator, including the Principal Investigator and/or any sub-Investigators, directly involved in the treatment or evaluation of subjects may be requested to provide a financial disclosure. All relevant documentation will be filed in the Study Master File.

13.4.3 Costs for Subjects

After the initial screening procedures in the community, the subjects' travels costs will be covered depending on the particular practices in the investigational centre with regard to payment of taxi fares, use of a study-specific vehicle or reimbursement at a flat rate, etc. Missed days of work due to participation in the study may be compensated, depending on local procedures and if permitted by the regulatory authorities and/or ethics committee(s). Accommodation, meals, toiletries, laundry and entertainment (such as television) during the In-house Period and any overnight stays at the investigational centre will also be provided free of charge to the subject.

All examinations, medication, including contraception, and medical care are part of the study and will be paid for by the Sponsor.

13.5 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the Sponsor and Investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in accordance with applicable local laws and regulations, including those regarding public health measures (e.g. COVID-19).

Documented approval from the regulatory authorities and ethics committee(s) will be obtained before the start of the study, in accordance with GCP, local laws and regulations. When necessary, an extension, amendment or renewal of the approval from the regulatory authorities and ethics committee(s) will be obtained and forwarded to the Sponsor as well. The responsible unit (e.g. the ethics committee, head of the investigational centre/medical institution) must supply to the Sponsor, upon request, a list of the members of each ethics committee involved in the vote and a statement to confirm that the ethics committee is organised and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in the protocol is required for all aspects of study conduct; the Investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the Sponsor or the Investigator without agreement by both parties. However, the Investigator or the Sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to the subjects without prior approval/favourable opinion from the Sponsor and/or the regulatory authorities. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the regulatory authorities and ethics committee(s)/head of medical institution/Sponsor. Any deviations from the protocol must be explained and documented by the Investigator.

13.6 Subject Information and Informed Consent

All relevant information on the study will be summarised in a comprehensive study information document and ICF, provided by the Sponsor or the investigational centre.

The informed consent process will begin only after obtaining approval from the regulatory authorities and ethics committee(s) applicable for the investigational centre. It will be conducted before screening of subjects, and it will include both community and individual consent (see also Section 9.2.2). The informed consent process will be conducted as per the detailed procedure described in the Study Operations Manual/SOPs.

13.7 Publication Policy and Use of Study Data

The study will be registered with a recognised clinical study registry, e.g. www.clinicaltrials.gov, Pan African Clinical Trials Registry.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilise them in various ways, such as for submission to the regulatory authorities.

The final clinical study report will be the responsibility of the Sponsor and will be submitted to the regulatory authorities and ethics committee(s), if required by these bodies, when available.

The Sponsor encourages the communication and/or publication of the results, in accordance with the terms of the Clinical Trial Agreement.

13.8 Insurance

The Sponsor will cover any claims made by a subject, or by a family member or legal representative on his/her behalf, for damage resulting directly from the study and will also indemnify the Investigator against any liability resulting from such claims. Coverage of the damage to the subject and indemnification of the Investigator by the Sponsor will not apply if the damages to the subject result from negligence or intentional misconduct on the part of employees or agents of the institution/the investigational centre(s). Such claims will be covered by insurance contracted by the institution/investigational centre(s).

13.9 Confidentiality and Protection of Privacy

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available.

Subject names will not be entered in the eCRF or any document or digital file supplied to the Sponsor. The screening number / randomisation number will be used as identification and, if the subject's name appears on any other document or file, e.g. pathologist report, etc., it will be redacted before a copy of the document is supplied to the Sponsor. Images captured during the study according to this protocol, e.g. photographs of ocular fundi, parasitological images, photographs of abnormalities found during physical examination, including skin lesions, will be coded using screening number/randomisation number as described above, and no images from which a subject can be visually identified will be transmitted outside of the investigational centre. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that only authorised persons will have access to their information and that all personal information will be handled in strictest confidence and in accordance with data protection laws. Also that the Sponsor and their authorised representatives, the ethics committee(s) and regulatory authorities may inspect their medical records to verify the information collected.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain master subject log to enable subjects to be identified.

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15 Appendices

List of Appendices

Appendix 1. Schedule of Events for Part 1

Table 7. Schedule of Events for Part 1

All study days / times are calculated relative to the time of administration of IMP on Day 0, i.e. 0d00h00m.

Time (and window if allowed)	**Screening[1]**	**In-house**								
	Up to 8 weeks before first intake of IMP	**D0[2]**	**D1[2]**	**D3[2]**	**D6[2]**	**D13[2, 24]**	**Month 3 (±1week)[2]**	**Month 6 (±1Month)[2]**	**EOS**	**Early Termination**
Subject information and informed consent, allocation of screening number[3]	X									
Demographic data and medical history, including prior and current medication	X									
Review of inclusion and exclusion criteria	X	X								
Skin snips[4,]	X (repeat if >30 days before 1st intake of IMP*)						X	X		X
Parasitology[5]	X (repeat if >3 days before 1st intake of IMP*)									
Nodule palpation[6]	X							X		X
Physical examination[7]	X (repeat if >3 days before 1st intake of IMP*)	X[9]		X[9]	X[9]	X	X	X		X
Brief neurological examination[8]	X (repeat if >3days before 1st intake of IMP*)	X		X	X	X	X	X		X
Pregnancy test (WOCBP only)[10]	X (repeat if >2 days before 1st intake of IMP)					X	X	X		X
Check birth control and date of last menstrual period[11]	X (repeat if >3 days before 1st intake of IMP*)					X	X			

Time (and window if allowed)	Screening[1]	In-house								
	Up to 8 weeks before first intake of IMP	D0[2]	D1[2]	D3[2]	D6[2]	D13[2, 24]	Month 3 (±1week)[2]	Month 6 (±1Month)[2]	EOS	Early Termination
Vital signs[12]	X (repeat if >3 days before 1st intake of IMP*)	X		X	X	X	X			X
Ophthalmological examination[,13]	X[6] (repeat if >30 days before 1st intake of IMP)					X	X	X		X
Skin examination[14]	X					X	X	X		X
12-lead safety ECG [15]	X (repeat if >3 days before 1st intake of IMP*)			X	X	X				X[15]
Laboratory safety tests[16]	X (repeat if >3 days before 1st intake of IMP*)			X	X	X	X			X
Alcohol breath test and urinary drug screen	X (repeat if >2 days before 1st intake of IMP)									
Randomisation		X								
IMP administration[17]		Every day – Direct Observed Treatment								
PK of IMPs in blood[, 21]		X	X	X	X	X				
Ivermectin administration								X[18]		X[18]
AE monitoring[19,20]	X	X	X	X	X	X	X	X	X	X
Concomitant medication monitoring		X	X	X	X	X	X	X	X	X
Exploratory samples [22]		X				X		X		X
Nodulectomy[23]								X[23]		X[23]
Post-nodulectomy wound care[25]									X	

1. Some screening procedures will be conducted in the subjects' communities.
2. For each subject, a given procedure should as far as possible be performed at the same time of day every time it is scheduled throughout the study to minimise variability. Also note that on IMP administration days, some procedures must be performed pre-IMP intake and others post-IMP intake. See Section 9.2.4 for details, and other footnotes herein.
3. Screening procedures will be performed only after obtaining the main written informed consent
4. Skin snips will be used to assess *O. volvulus* skin microfilarial density and depletion of Wolbachia in the microfilaria at the indicated time-points. Four skin snips per time-point (iliac crests and calves on both sides).

5. Blood sampling; including evaluation in blood of *Wuchereria bancrofti*, *Mansonella perstans* and *Loa loa*.
6. Nodule palpation and documentation of *Onchocerca* nodules.
7. Details of the physical examinations will be specified in the Study Operations Manual. To include height and weight at Screening, and within 2 days prior to first intake of IMP.
8. A short symptom-directed neurological examination will be conducted. Details of the examination will be specified in the Study Operations Manual.
9. At the time-points indicated, a shortened symptom-directed physical examination will be conducted. Details of the examination will be specified in the Study Operations Manual.
10. Pregnancy testing may be urine or serum, except for test at screening at the site and at Day 13 visit (or Early Termination Visit if done before Day 13), which must be serum. In case a repeat is needed during screening at the site, test can be urine providing the initial testing was serum and this was approved by the sponsor. Test at the Day 13 visit will be done at least 24 hours after the last IMP intake.
11. The Investigator will arrange for a highly effective form of birth control (as detailed in Section 8.2) if required. Must be discussed at screening and checked within 2 days prior to the first intake of IMP and checked at the time-points indicated and documented. In the event of delayed menstrual period for over one month between menstruations, confirmation of absence of pregnancy with a pregnancy test is mandatory. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.
12. Supine blood pressure (SBP, DBP), supine heart rate, respiratory rate and temperature.
13. Ophthalmological findings from examinations including ocular symptoms, ocular examinations including ocular alignment, mobility and pupillary response, visual function (visual acuity, visual field, colour vision), retinal examination and fundus photography, slit lamp examination of anterior and posterior segment and intraocular pressure. Eye microfilarial count and data for clinical outcomes in the eye will be recorded during the ophthalmological examination.
14. Assessments for clinical outcomes in the skin (see Study Operations Manual for details) to be performed during physical examinations where the time-points coincide.
15. ECGs will be recorded in triplicate (with 1 minute between recordings) except at D3, which will be single. ECGs will be performed 1-2 hours after intake of the IMP. ECG at early termination is only applicable if early termination is before Month 3.
16. Blood and urine samples for clinical laboratory safety tests (haematology, biochemistry, & urinalysis (plus urine microscopy where indicated if urinalysis is abnormal and clinically significant).
17. IMPs will be administered daily from D0 to D13 on site. IMPs dispensation will be done on D0, D3 and D7 via the IRT system.
18. Administration of ivermectin to all subjects. Only after completion of all the procedures of the 6-month follow-up visit, and after nodulectomy and negative pregnancy test. It can also be administered at the early termination visit at the discretion of the Investigator. Ivermectin will also be available for administration as Rescue Medication, at the Investigator's discretion, in the event of clinically significant worsening of symptoms and/or signs related to onchocerciasis at any time during the study.18.AE monitoring will be performed as specified in Section 9.3.4 and will include scheduled questioning at the indicated time-points.
19. AE collection from signature of Informed Consent onwards. AE monitoring will be performed as specified in Section 9.3.4 and will include scheduled questioning at the indicated time-points.
20. In the event of certain AEs considered to be associated with the IMP, additional examinations may be conducted in order to better interpret the AE, including safety laboratory, PK, ophthalmological, physical, neurological, and parasitological (eye and skin) examinations.
21. Blood samples for dry blood spot assay (PK) of ABBV-4083 and albendazole sulfoxide will be collected on Day 0: 0h (any time before dosing), 1h, 2h, 3h, 4h, 6h and 12h (+/- 15 minutes for all) ; and Day 1 at 0h (up to 30 min prior dosing). Samples on Day 3, 6 and 13 will be collected between 2 and 4 hours after dosing.
22. Blood and urine samples will be collected at the time-points indicated and stored for future analysis (for example: biomarkers, immunological markers testing). Note: in addition, where feasible, tissue samples collected from other procedures during the study (e.g. skin, nodules etc.) will also be stored after analysis. Subjects have the possibility to opt out of exploratory samples.
23. Nodulectomy must be conducted only after completion of the procedures at the Month 6 visit.
24. In-house Period will have one additional day on D13 for observation post last dose and to perform pregnancy test at the end of exposure period.

25. Post-nodulectomy wound care will continue for up to approx. 2 weeks. The subject may go back to the community or may stay at the investigational site for logistic reasons or if medically indicated. End of Study visit will be 2 weeks after nodulectomy +/- 2 weeks. The visit may be performed in the community.

* Repeat period can be extended to 7 days in exceptional circumstances, with prior agreement of the Sponsor (exception of pregnancy test which must be repeated within 2 days and can be urine if serum test was already done)

Appendix 2. Schedule of Events in Part 2

Table 8. Schedule of Events in Part 2

All study days / times are calculated relative to the time of administration of IMP on Day 0, i.e. 0d00h00m.

Time (and window, if allowed)	Screening[1]	In-house				Out-patient						
	Up to 8 weeks before first intake of IMP[3]	D0[2]	D1[2]	D6[2]	D13[2,24]	Month 3 (±1 wk)[2]	Month 6 (±1 month)[2]	Month 12 (±1 month)[2]	Month 18 (±1 month)[2]	Month 24 (±1 month)[2]	EOS[25]	Early Termination
Subject information and informed consent, allocation of screening number[3]	X											
Demographic data and medical history, including prior and current medication	X											
Review inclusion and exclusion criteria	X	X										
Skin snips[4]	X (repeat if > 30 days before first intake of IMP)					X	X	X	X	X		X
Parasitology[5]	X (repeat if > 3 days before first intake of IMP*)											
Nodule palpation[6]	X						X[A]			X		X
Physical examination[7]	X (repeat if > 3 days before first intake of IMP*)			X[9]	X[9]	X	X	X	X	X		X
Brief neurological examination[8]	X (repeat if > 3 days before first intake of IMP*)			X	X	X	X	X	X	X		X
Pregnancy test (WOCBP only)[10]	X (repeat if > 2 days before first intake of IMP)				X	X	X	X	X	X		X
Check birth control and document last menstrual period[11]	X (repeat if > 3 days before first intake of IMP*)				X	X	X	X				

Time (and window, if allowed)	Screening[1]	In-house				Out-patient						
	Up to 8 weeks before first intake of IMP[3]	D0[2]	D1[2]	D6[2]	D13[2,24]	Month 3 (±1 wk)[2]	Month 6 (±1 month)[2]	Month 12 (±1 month)[2]	Month 18 (±1 month)[2]	Month 24 (±1 month)[2]	EOS[25]	Early Termination
Vital signs[12]	X (repeat if > 3 days before first intake of IMP*)	X		X	X							X
Ophthalmological examination[13]	X (repeat if > 30 days before first intake of IMP)					X	X	X	X	X		X
Skin examination[14]	X					X	X	X	X	X		X
12-lead safety ECG [15]	X (repeat if > 3 days before first intake of IMP*)			X	X							X[15]
Laboratory safety tests[16]	X (repeat if > 3 days before first intake of IMP*)			X	X	X						X
Alcohol breath test and urinary drug screen	X (repeat if > 2 days before first intake of IMP)											
Randomisation		X										
IMP administration[17]		Every day – direct observed intake					X					
PK of IMPs in blood[21]		X	X	X	X							
Rescue medication (ivermectin)									X[18]	X[18]		X[18]
AE monitoring[19,20]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication monitoring		X	X	X	X	X	X	X	X	X	X	X
Exploratory samples[22]		X			X			X	X	X		X
Nodulectomy							X[A,23]			X[23]		X[23]
Post-nodulectomy wound care[25]											X	

A. If Alternative scenario

1. Some screening procedures will be conducted in subjects' communities.
2. For each subject, a given procedure should as far as possible be performed at the same time of day every time it is scheduled throughout the study to minimise variability. Also note that on IMP administration days, some procedures must be performed pre-IMP intake and others post-IMP intake. See Section 9.2.4 for details and other footnotes herein.
3. Screening procedures will be performed only after obtaining the main written informed consent
4. Skin snips will be used to assess O. *volvulus* skin microfilarial density at the indicated time-points.. Four skin snips per time-point (iliac crests and calves on both sides).
5. Blood sampling including evaluation in blood of *Wuchereria bancrofti*, *Mansonella perstans* and *Loa loa*.
6. Nodule palpation and documentation of onchocerca nodules.
7. Details of the physical examinations will be specified in the Study Operations Manual. To include height and weight at Screening, and within 2 days prior to first intake of IMP.
8. A short symptom-directed neurological examination will be conducted. Details of the examination will be specified in the Study Operations Manual.9. At the time-points indicated, a shortened symptom-directed physical examination will be conducted. Details of the examination will be specified in the Study Operations Manual.
10. Pregnancy testing may be urine or serum, except for test at screening at the site and at Day 13 visit, (or Early Termination Visit if done before Day 13) which must be serum. In case a repeat is needed during screening at the site, test can be urine providing the initial testing was serum and this was approved by the sponsor. Test at the Day 13 visit will be done at least 24 hours after the last IMP intake.
11. The Investigator will arrange for a highly effective form of birth control (as detailed in Section 8.2) if required. Must be discussed at Screening, checked within 2 days prior to first intake of IMP, checked at the time-points indicated and documented. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy with a pregnancy test is mandatory. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.
12. Supine blood pressure (SBP, DBP), supine heart rate, respiratory rate and oral temperature
13. Ophthalmological examinations: full ophthalmological examination includes ocular symptoms, ocular examinations including ocular alignment, mobility and pupillary response, visual function (visual acuity, visual field, colour vision), retinal examination and fundus photography, slit lamp examination of anterior and posterior segments and intraocular pressure. Eye microfilarial count and data for clinical outcomes in the eye will be recorded during the ophthalmological examination.
14. Assessments for clinical outcomes (see Study Operations Manual for details) in the skin to be performed during physical examinations where the time-points coincide.
15. 12-lead ECGs will be recorded in triplicate with 1 minute between recordings at all time-points. ECGs will be performed 1-2 h after intake of the IMP. ECG at early termination is only applicable if early termination is before Month 3.
16. Blood and urine samples for clinical laboratory safety tests (haematology, biochemistry & urinalysis (plus urine microscopy where indicated if urinalysis is abnormal and clinically significant).
17. IMPs will be administered daily on site and IMPs dispensation will be done via the IRT system. Treatment duration and IMPs dispensation scheme will be confirmed before start of the Part 2, depending on the regimen selected.
18. Administration of ivermectin must be only after completion of the procedures scheduled at the visit (including nodulectomy where scheduled), and after a negative pregnancy test. Rescue medication (ivermectin) will be offered at the investigator discretion to administer if worsening symptoms and/or signs related to onchocerciasis at any time throughout the study and/or to patients with increased mean microfilaria in the skin at Month 18, compared to the Month 12 mean value.
19. AE collection from signature of Informed Consent onwards. AE monitoring will be performed as specified in Section 9.3.4 and will include scheduled questioning at the indicated time-points.
20. In the event of certain AEs considered to be associated with the IMP, additional examinations may be conducted in order to better interpret the AE, including safety laboratory, PK, ophthalmological, physical, neurological and parasitological (eye and skin) examinations.
21. Blood samples for dry blood spot assay (PK) of ABBV-4083 and albendazole sulfoxide will be taken on Day 0: 0h (any time before dosing), 1h, 2h, 3h, 4h, 6h and 12h (+/- 15 minutes for all); and Day 1 at 0h (up to 30 min prior dosing. Samples on Day 6 and 13 will be collected between 2 and 4 hours after dosing. Schedule to be confirmed based on data from Part 1

22. Blood and urine samples will be collected at the time-points indicated and stored for future analysis (for example: biomarkers, immunological markers testing). Note: in addition, where feasible, tissue samples collected from other procedures during the study (e.g. skin, nodules etc.) will also be stored after analysis. Subjects have the possibility to opt out of exploratory samples.
23. Nodulectomy must be performed only after completion of the other procedures at the visit.
24. In-house Period will have one additional day on D13 for observation post last dose and to perform pregnancy test at the end of exposure period.
25. Post-nodulectomy wound care will continue for up to approx. 2 weeks. The subject may go back to the community or may stay at the investigational site for logistic reasons or if medically indicated. End of Study visit will be 2 weeks after nodulectomy. The visit may be performed in the community

* Repeat period can be extended to 7 days in exceptional circumstances, with prior agreement with the Sponsor (exception of pregnancy test which must be repeated within 2 days and can be urine if serum test was already done)

Appendix 3. Total Blood Volume to be Collected in Part 1

The blood volume planned to be collected from each subject during the Part 1 of this study is detailed in Table 9, rounded up to the nearest 1 mL. Additional samples may be required in the event of AEs.

Table 9. Total Blood Volume in Part 1

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Pregnancy serum test	2	Screening and Day 13:0 (on biochemistry tube)	0
Parasitology - microscopy Parasitology - RDT	1	4 1	5
Haematology	5	4	20
Biochemistry	5	5	25
Pharmacokinetics	11	1	11
Exploratory samples	3	5	15
Cannula discard	7	1	7
Total blood volume to be collected in Part 1 per subject			**84**

RDT: rapid diagnostic test

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

Appendix 4. Total Blood Volume to be Collected in Part 2

The blood volume planned to be collected from each subject during Part 2 of the study is detailed in Table 10, rounded up to the nearest 1 mL. Additional samples may be required in the event of AEs. The total blood volume to be taken during the study will be confirmed once the regimens for Part 2 have been selected.

Table 10. Total Blood Volume in Part 2 - Phase II

Test	Planned number of tests	Volume (mL)	Total planned blood volume (mL)
Pregnancy serum test	2	Screening and Day 13:0 (on biochemistry tube)	0
Parasitology - microscopy Parasitology - RDT	1	4 1	5
Haematology	4	4	16
Biochemistry	4	5	20
Pharmacokinetics	10	1	10
Exploratory samples	5	5	25
Cannula discard	7	1	7
Total blood volume to be collected in Part 2 per subject			**84**

RDT: rapid diagnostic test

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

Appendix 5. Laboratory Analyses

Detailed information about the collection, processing, storage and shipment of the samples will be provided in the laboratory manual and/or Study Operations Manual. Information on the parameters to be analysed and the laboratories to be used is presented in Table 11.

Table 11. Parameters of Laboratory Analyses

Parameters (by category)	Sample destination
Haematology: haemoglobin, haematocrit, platelets, white blood cells (WBC) and differential, red blood cells (RBC).	Study Investigational sites
Biochemistry: aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP), glucose, creatinine, eGFR, blood urea nitrogen (BUN), total bilirubin, albumin, total protein, chloride, sodium, potassium and calcium in serum.	Study Investigational sites
Urinalysis – dipstick, multistick and microscopy: glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrite	Study Investigational sites
Parasitological co-infections (microscopy): Blood: lymphatic filariasis*, Mansonella perstans, and Loa loa*	Study Investigational sites
Urine drug screen: Drugs of abuse screen	Study Investigational sites
Serum pregnancy test: Beta-HCG	Study Investigational sites
Urine pregnancy test: Beta-HCG	Study Investigational sites and Participants' communities
Alcohol test: Breath test	Study Investigational sites
Pharmacokinetic analyses in blood: Parameters are specified in Section 5.6	Attn: AbbVie Sample Receiving [redacted] Delivery Services 1150 S. Northpoint Blvd. Waukegan, IL 60085 E-mail: sample.receiving@abbvie.com
Microfilarial density from skin snips *O. volvulus* *Mansonella streptocerca*	Study Investigational sites
Nodule assessment	Institute of Medical Microbiology, Immunology and Parasitology; University Hospital Bonn, Germany
Exploratory samples Plasma Urine Remaining samples from those collected from scheduled protocol procedures	Study Investigational sites May be transferred for logistical purposes (longer term storage) to another location with prior agreement of Ethical Committees and Regulatory Authority.

Appendix 6. Adverse Event Severity Grading Reporting for DNDi-TYL-01 Clinical Trial

Please refer to most current document “Adverse Event Severity Grading Reporting for DNDi-TYL-01” attached to the protocol.

Appendix 7. Permitted and non-permitted birth control methods in DNDi-TYL-01

Permitted birth control methods in DNDI-TYL-01

Methods which may be considered as "highly effective" (failure rate of less than 1% per year when used consistently and correctly):

(based on the Clinical Trial Facilitation Group recommendations from The Medicines and Healthcare Products Regulatory Agency website related to contraception and pregnancy testing in clinical trials, dated 15 September 2014).

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable

- intrauterine device (IUD)

- intrauterine hormone-releasing system (IUS)

- bilateral tubal occlusion

- vasectomised partner[1]

- sexual abstinence[2]

[1] Vasectomised partner is a highly effective birth control method provided the partner is the sole sexual partner of the WOCBP and that the vasectomised partner has received medical assessment of the surgical success.

[2] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Non-Permitted birth control methods in DNDI-TYL-01

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

- male or female condom with or without spermicide[1]

- cap, diaphragm or sponge with spermicide[1]

- Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.

[1] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are not considered highly effective birth control methods and therefore are not permitted in DNDI-TYL-01.

Appendix 8. Prohibited medications in DNDi-TYL-01

I. Prohibited medication before starting the study (see also Section 6.2)

- within 2 years prior to start of IMP administration: moxidectin;
- within 1 year prior to start of IMP administration: more than 2-week course of anti-*Wolbachia* treatments, i.e. doxycycline, minocycline, rifapentine or rifampicin;
- within 6 months prior to start of IMP administration: ivermectin;
- within 3 months prior to start of Screening (or within 5 times the half-life of the drug tested): any investigational drug;
- within 4 weeks prior to start of IMP administration: any vaccination;
- Within 14 days prior to start of IMP administration:
  - any medication (with the exception of diclofenac, paracetamol, ibuprofen and aspirin), herbal preparation or food supplement;
  - strong CYP3A inhibitors or inducers including but not limited to ritonavir[c], ketoconazole[c], rifampicin, phenytoin, phenobarbital, carbamazepine, cimetidine[c] (or within 10 half-lives, whichever is longer);
  - other drugs known to interact with albendazole such as praziquantel[c], theophylline[c] or dexamethasone[c] (or within 10 half-lives, whichever is longer);

II. Prohibited medication throughout the entire study[a]

Prohibited medication throughout the entire study include any medication that may have an impact on the study objective. Specifically, medication with anti-filarial or anti-Wolbachia effects are prohibited, including:

- ivermectin, excluding post-study ivermectin or rescue ivermectin as detailed in Section 8.3.
- moxidectin,
- doxycycline,
- minocycline,
- rifampicin,
- rifapentine.

III. Prohibited medications during the first 28 days after the last IMP administration

- Albendazole (however it is permitted thereafter, one dose per year in MDA)

IV. Prohibited medication during the treatment period

Up to 24 hours after the final dose of IMP, medication, herbal remedies or food supplements, that could affect the PK and/or PD of ABBV-4083 and/or albendazole are prohibited.

- Any CYP3A and/or P-gp inhibitors or inducers, such as:
  - ritonavir[c],
  - ketoconazole[c],
  - rifampicin[b],
  - phenytoin[b],
  - phenobarbital[b],
  - carbamazepine[b],
  - cimetidine[c],
  - others known to interfere with the CYP3A and/or P-gp metabolic pathways (the US FDA tables of Substrates, Inhibitors and Inducers[b] will be used as a reference, and included in the Study Operations Manual for reference).

- Drugs known to interact with albendazole, such as
  - praziquantel[c],
  - dexamethasone[b]
  - theophylline[c]

a. Subjects taking these medications during the study will not be included in the PP population for analysis and will be imputed as failures in analyses of the primary and secondary endpoints in the ITT population.

b. Subjects taking these medications during the treatment period (or for 14 days before) will not be included the PP population for analysis but will not be imputed as failures in analyses of the primary and secondary endpoints in the ITT population.

c. Subjects taking these medications during the treatment period (or for 14 days before) will be included in the PP population for analysis and will not be imputed as failures in analyses of the primary and secondary endpoints in the ITT population.