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 $\geq$ 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; $\leq$ 6 months prior to IMP administration; and/or o doxycycline, $\leq$ 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, $\leq$ 1 year prior to IMP administration: more than 2-week course; and/or o moxidectin, $\leq$ 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).