Statistical Analysis Plan

for Study B18-894/DNDi-TYL-01

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

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

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses of Part 1 only for ABBV-4083 Study B18-894/DNDi-TYL-01 "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." Part 2 will have a separate clinical database with a separate SAP and database lock.

Part 1 of Study B18-894/DNDi-TYL-01 investigates the safety, tolerability, efficacy for duration-ranging and pharmacokinetics of ABBV-4083 with or without albendazole in subjects infected with *Onchocerca volvulus*.

The analyses of pharmacokinetic endpoints and their relationship to efficacy and safety endpoints will not be covered in this SAP.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

Unless noted otherwise, all analyses will be performed using SAS Version 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

All analyses in this SAP are consistent with what is described in the study protocol unless otherwise noted in Section 13.0.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The primary objectives are to:

- determine whether treatment with ABBV-4083 or ABBV-4083 + albendazole effectively depletes *Wolbachia* endobacteria 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* endobacteria in adult female worms at Month 6 by immunohistology.

The primary hypothesis for Part 1, proof-of-concept, is that more worms will have *Wolbachia* endobacteria (hereafter only referred to as *Wolbachia*) depletion at Month 6 in subjects who completed treatment with ABBV-4083 for 7 days, ABBV-4083 for 14 days, ABBV-4083 for 7 days + albendazole for 7 days, or ABBV-4083 for 7 days + albendazole for 3 days than in subjects treated with albendazole for 7 days among all subjects who completed treatment and had live female worms from nodulectomies at Month 6. The associated estimand is the odds ratio of *Wolbachia* depletion in a live female adult worm between subjects treated with one of the active regimens (ABBV-4083 for 7 days, ABBV-4083 for 14 days, ABBV-4083 for 7 days + albendazole for 7 days, or ABBV-4083 for 7 days + albendazole for 3 days) and the control regimen (albendazole for 7 days) in the Per Protocol population (see Section 4.0). Subjects who did not complete treatment, did not have Month 6 nodulectomy data, or took prohibited medications will be excluded.

The primary hypothesis for the combination rule is that more worms will have *Wolbachia* depletion at Month 6 in subjects treated with ABBV-4083 for 7 days + albendazole for 7 days than in subjects treated with ABBV-4083 for 7 days or those treated with albendazole for 7 days among all subjects who completed treatment and had live female worms from nodulectomies at Month 6. If the combination arm of ABBV-4083 for 7 days + albendazole for 3 days is to advance to Part 2 of Study B18-894/DNDi-TYL-01 and ABBV-4038 for 7 days + albendazole for 7 days is not, the combination rule in Part 1 will instead be tested for ABBV-4083 for 7 days + albendazole for 3 days. The associated estimand is the odds ratio of *Wolbachia* depletion in a live female adult worm between subjects treated with the combination regimen (ABBV-4083 for 7 days + albendazole for 7 days, or ABBV-4083 for 7 days + albendazole for 3 days, depending on Part 2 as described before) and the single drug regimen (ABBV-4083 for 7 days, and albendazole for 7 days) in the Per Protocol population (see Section 4.0). Subjects who did not

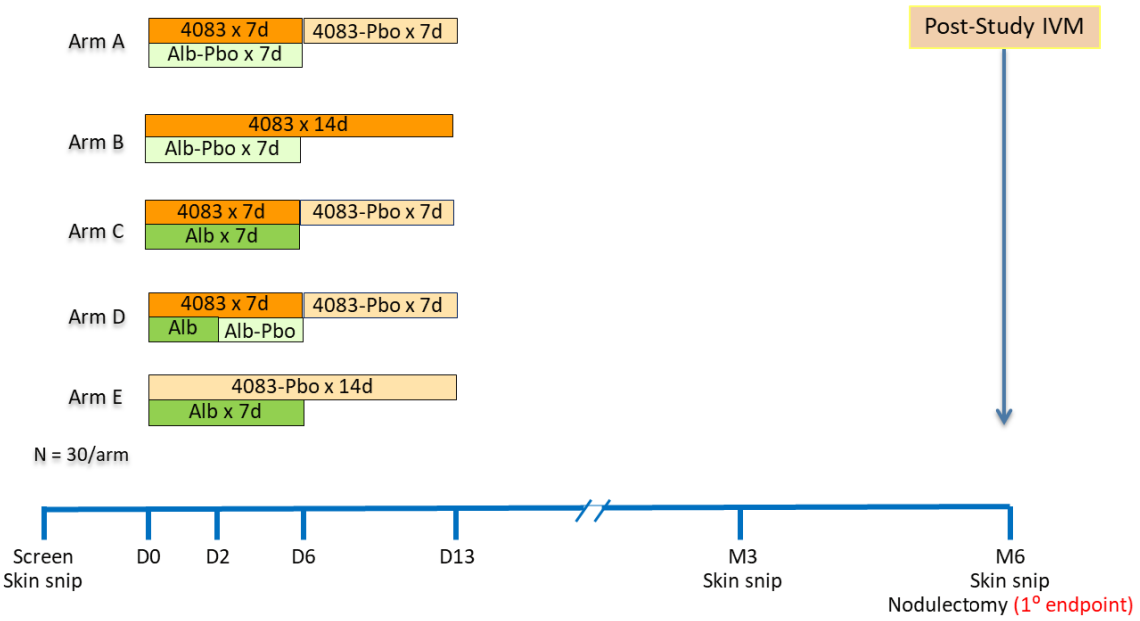
complete treatment, did not have Month 6 nodulectomy data, or took prohibited medications will be excluded.

2.2 Study Design Overview

A total of 150 subjects will be enrolled into five treatment arms with 30 subjects for each arm. The treatment period will last for 14 days and the post-treatment period will follow till Month 6. Post-study ivermectin that kills microfilaria will be given to all participants after nodulectomy at Month 6.

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



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

2.3 Treatment Assignment and Blinding

Subjects will be randomized continuously 1:1:1:1:1 into one of five parallel treatment arms through an Interactive Response Technology (IRT) system. Randomization will be

stratified by the number of operable sites with onchocercomata (one site vs. more than one site).

The five treatment arms are defined as follows:

- Arm A: 7 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 matching placebo
- Arm B: 7 days of ABBV-4083 400 mg + albendazole matching placebo followed by 7 days of ABBV-4083 400 mg
- Arm C: 7 days of ABBV-4083 400 mg + albendazole 400 mg followed by 7 days of ABBV-4083 matching placebo
- Arm D: 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: 7 days of ABBV-4083 matching placebo + albendazole 400 mg followed by 7 days of ABBV-4083 matching placebo

The treatment assignment will remain blinded to the Investigator, as well as clinical, pharmacy, and laboratory personnel, and the Sponsor, including statistics and data management personnel and the study monitor, until the final database lock, after all Part 1 subjects are followed to Month 6 or have prematurely discontinued from follow-up.

Toxicity of the treatments will be monitored throughout the study. If > 10% of the subjects in any arm meet any of the protocol-specified toxicity criteria after 15 subjects are enrolled in each arm, the Data and Safety Monitoring Board (DSMB) may recommend halting enrolment into arms of the same or longer duration with or without albendazole and continuing enrolment in those arms of the shorter duration. 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 received 400 mg QD ABBV-4083 in the halted arm

and have not experienced dose-limiting toxicity will be kept on the same dose until treatment completion.

If Arm A, B, C, or D is closed and then reopened using ABBV-4083 at 300 mg QD, the subjects previously given ABBV-4083 at 400 mg QD in the closed arm will be excluded from all efficacy analyses (Section 9.1). Throughout this SAP, Arm A, B, C, D will be used to denote treatment regimens using either ABBV-4083 at 400 mg or 300 mg QD. For the actual treatment assignment, Arm A, B, C, D will be renamed as Arm F, G, H, I, respectively, upon reopening. For safety analyses, all arms will be summarized separately, even if any of them is closed during the study (Section 10.0). If all of Arms A, B, C, and D are closed, and any of Arms F, G, H, I are opened, the control arm (albendazole alone), Arm E, will be replaced with Arm J which uses the same pill count as Arms F, G, H, I to maintain blinding of the control arm. For all analyses, subjects from Arm E and Arm J will be combined.

2.4 Sample Size Determination

To test the primary hypothesis for the proof of concept, an alternating logistic regression will be used to compare the proportion of live female adult worms without *Wolbachia* at Month 6 between each of the four active arms (Arm A, B, C, or D) and the control arm (Arm E), 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, 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),[1] 17 subjects will provide 88% power to detect the difference between an active arm (Arm A, B, C, or D) where 70% of worms are without *Wolbachia* and the control 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)[2] for binary outcomes and was given as ICC = 0.54 for simulated arms where 70% or 30% of the worms are without *Wolbachia*.

To test the primary hypothesis for the combination rule, an alternating logistic regression will be used to compare the proportion of live female adult worms without *Wolbachia* at Month 6 between the combination arm (Arm C or D) and the two single drug arms (Arm A and E) separately, 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). 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 there would be little variation among subjects with an overall high response rate. 30 subjects will be enrolled per arm to account for 17% drop out by Month 6.

3.0 Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is the status of each live female adult worm as without *Wolbachia*, assessed by immunohistology of nodules collected after nodulectomy at Month 6.

3.2 Secondary Endpoints

There is no key secondary endpoint in Part 1 of Study B18-894/DNDi-TYL-01. The other secondary efficacy endpoints are:

- 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 at Months 3 and 6;

- the reduction from baseline in skin microfilarial density (defined as the mean number of microfilariae/mg per subject) at Months 3 and 6;
- the status of each nodule that contains at least 1 live female adult worm as without *Wolbachia* assessed by PCR at Month 6.

3.3 Exploratory Endpoints

The exploratory efficacy endpoints are:

- the absence of *Wolbachia* in skin microfilariae per subject by PCR at all timepoints;
- the decline from baseline in number of *Wolbachia* (assessed by PCR) in skin microfilariae per subject at all timepoints;
- 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 timepoints when ophthalmological or skin examinations are performed.

3.4 Safety Endpoints

The safety endpoints are based on the following assessments:

- Adverse Event (AE) assessment (all reported AEs);
- Vital signs;
- 12-lead ECG;
- Clinical laboratory parameters: hematology and biochemistry.

4.0 Analysis Populations

The following population sets will be used for the analyses.

The Intention-to-Treat (ITT) population includes all randomised subjects who received at least one dose of study drug. The ITT population will be used for all non-primary efficacy estimands. Subjects will be included in the analysis according to the treatment arm to which they were randomised.

The Per-Protocol (PP) population will include all ITT subjects who had Month 6 nodulectomy (ND6M) with live female adult worms, who completed treatment and did not take prohibited medication(s) during the study. Treatment completion is defined as taking at least 6 out of 7 days of ABBV-4083 in Arm A, 12 out of 14 days of ABBV-4083 in Arm B, 6 out of 7 days of ABBV-4083 + albendazole in Arm C, 6 out of 7 days of ABBV-4083 and all 3 days of albendazole in Arm D, and 6 out of 7 days of albendazole in Arm E. Prohibited medications (Appendix B) include those with anti-filarial or anti-*Wolbachia* effect taken at any time during the study, or strong CYP3A inducers or dexamethasone taken during the treatment period. The PP population will be used as the primary population for testing the two primary hypotheses (Section 2.1).

The Safety population includes all randomized subjects who received at least one dose of study drug. Subjects will be included in the analysis according to treatment as randomized. The Safety population is the same as the ITT population.

5.0 Subject Disposition

The number of subjects in each of the following categories will be summarized by site and overall for each treatment arm and overall:

- Subjects who were screened;
- Subjects who were randomized;
- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment (ABBV-4083, albendazole, and the overall regimen [i.e., both study drugs]);
- Subjects who prematurely discontinued study drug (ABBV-4083, albendazole, and at least one of ABBV-4083 or albendazole);

- Subjects who completed the protocol-defined follow-up period;
- Subjects who prematurely discontinued study follow-up;
- Subjects in the PP population.

The number and percentage of subjects, overall and by treatment arm, who prematurely discontinued study drug (ABBV-4083, albendazole, and at least one of ABBV-4083 or albendazole) will be summarized by primary reason for discontinuing study drug (ABBV-4083 and albendazole) and overall for discontinuing at least one of ABBV-4083 or albendazole. The number and percentage of subjects, overall and by treatment arm, who prematurely discontinued the study will also be provided.

The number and percentage of subjects, overall and by treatment arm, who interrupted study drug (ABBV-4083, albendazole, and at least one of ABBV-4083 or albendazole) will be summarized by primary reason for interrupting study drug (ABBV-4083 and albendazole) and overall for interrupting at least one of ABBV-4083 or albendazole.

6.0 Study Drug Duration and Compliance

For the Safety population, duration of treatment will be summarized by treatment arm and overall. Duration of treatment is defined for each subject as last dosing date minus first dosing date + 1 day. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, Q1, Q3, minimum, and maximum. In addition, the number and percentage of subjects by each treatment duration interval (1 to 7 days, 8 to 14 days, or > 14 days) will be summarized, and the number and percentage of subjects with duration long enough to meet the Per Protocol definition will also be summarized.

For the Safety population, treatment compliance will be summarized by treatment arm separately for ABBV-4083/matching placebo and albendazole/matching placebo. Treatment compliance is defined as the number of capsules that were taken divided by the number of capsules that should have been taken (56 capsules for 14 days of ABBV-4083/matching placebo at 400 mg QD, 42 capsules for 14 days of

ABBV-4083/matching placebo at 300 mg QD, 7 capsules for 7 days of albendazole/matching placebo). The mean, median, standard deviation, Q1, Q3, minimum, and maximum of treatment compliance will be summarized. In addition, the number and percentage of subjects with treatment compliance between 80% and 120% will also be summarized, excluding subjects with missing values in the denominator. A listing of each subject's treatment compliance will also be provided.

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the PP and ITT populations by treatment arm as well as overall. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum and maximum).

7.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, height, and body mass index (BMI). Categorical demographic variables include sex, race, age (< 40, or ≥ 40 years), weight (< 60 or ≥ 60 kg), and BMI (< 18, 18 to < 25, or ≥ 25 kg/m^2).

Baseline characteristics include symptoms of onchocerciasis disease (ocular or skin), number of operable sites with onchocercomata (continuous and categorical: 0, 1 or > 1), number of palpated nodules (continuous and categorical: 0, 1 or > 1), skin microfilarial density (continuous and categorical: ≤ 5 or > 5 mf/mg), district of residence (Kimpese, Masa, Masi-Manimba, Moanza, Nsonampangu, Pay Kongila, or Other), number of years resident in endemic area (continuous), number of previous ivermectin rounds (continuous and categorical 0, 1, or > 1), time since the last ivermectin administration (continuous and categorical, ≤ 1 year or > 1 year), parasitological co-infections (e.g., *Loa loa* or *Schistosoma haematobium*).

Baseline continuous laboratory values include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), creatinine clearance, estimated glomerular filtration rate (eGFR), total bilirubin, and albumin.

"Baseline" refers to the last non-missing observation before the first administration of study drug.

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment arm. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications. Anthelmintic medications taken prior to the initiation of study drug will not be included in the summary of concomitant medications.

8.0 Handling of Potential Intercurrent Events for the Primary Endpoint

The primary efficacy endpoint (defined in Section 3.1) will be analyzed in the PP and ITT populations and the following methods will be used to address potential intercurrent events:

- Subjects who did not complete treatment will be excluded from the PP population (definition of completion in Section 4.0). They will be included in the ITT population.
- Subjects who took prohibited medications (Appendix B) will be excluded from the PP population. They will be included in the ITT population, but subjects who took medications with an anti-filarial or anti-*Wolbachia* effect at any time during the study will be counted as failures in the ITT population (Section 9.2).
- Subjects who withdrew due to a safety issue (premature discontinuation of study or study treatment due to an adverse event related to either study drug) will be excluded from both the PP population and the ITT population analyses if they have no count of live female adult worms (no ND6M results or no live female adult worms in the ND6M results). If the subjects had live female adult worms in the ND6M results, they will be included in both the PP population and the ITT population analyses with any missing *Wolbachia* depletion results imputed as failures (Section 9.2).
- Subjects who prematurely discontinued from the study or study treatment for reasons independent of the treatment (for example, lost to follow-up, withdrew informed consent, or due to an adverse event not related to either study drug) will be excluded from both the PP population and the ITT population analyses if they have no count of live female adult worms (no ND6M results or no live female adult worms in the ND6M results). If the subjects had live female adult worms in the ND6M results, they will be included in the PP population analysis if not all *Wolbachia* depletion results were missing and they will be included in the ITT population analysis with any missing *Wolbachia* depletion results imputed through multiple imputation (Section 9.2).

9.0 Efficacy Analyses

9.1 General Considerations

The analyses for the primary endpoint will be conducted in both the PP population and the ITT population. However, the PP population will be the population used for the primary estimand comparisons. All other efficacy analyses will be conducted in the ITT population. The testing of the two primary hypotheses will be 2-sided at an alpha level of 0.10. No adjustment for multiple comparisons will be made.

The Primary Analysis will be performed after all subjects have completed the Month 6 Visit or have prematurely discontinued study follow-up. This will be the only and final analysis for the primary endpoint as well as all other efficacy endpoints.

If Arm A, B, C, or D is closed and then reopened using ABBV-4083 at 300 mg QD, only the new arm using 300 mg ABBV-4083 will be included in the efficacy analyses of this SAP. Efficacy summaries of the closed arms may be performed as ad hoc analyses.

9.2 Handling of Missing Data for the Primary Endpoint

First, subjects with no count of live female adult worms (no ND6M results or no live female adult worms in the ND6M results) will be excluded from the PP population and the ITT population analysis, because the primary endpoint is a worm-level endpoint about the *Wolbachia* status of a live female adult worm in the ND6M results.

Then, if a subject took prohibited medications with an anti-filarial or anti-*Wolbachia* effect (Appendix B) at any time during the study, all live female adult worms in that subject will be counted as having *Wolbachia* for the ITT population analyses, regardless of the observed *Wolbachia* status. All worms in such subjects will be excluded according to the definition of the PP population (Section 4.0).

Then, if a subject withdrew due to a safety issue (Section 8.0), all the live female adult worms that have missing *Wolbachia* status will be imputed as having *Wolbachia* for both

the PP population and the ITT population analyses. Any live female adult worm that has the observed *Wolbachia* status will be analyzed as observed.

Finally, if any live female adult worm still has missing *Wolbachia* status, the *Wolbachia* status will be imputed for the worms of those subjects in the ITT population analyses using the multiple imputation described below, but those worms will be excluded from the analyses for the PP population.

For multiple imputation, the missing *Wolbachia* depletion results will be generated in 30 datasets in SAS PROC MI (fully conditional specification). The logistic regression method will be used to impute the binary primary *Wolbachia* status for each live female adult worm with missing *Wolbachia* status. The imputation model will include treatment and the randomization stratification factor (Section 2.3) as covariates. The random seed for PROC MI will be the SAS numerical form of the first subject randomization date in the study. In case of non-convergence, the random seed will be updated by adding 100,000 at each attempt until convergence of model occurs. If the model will not converge due to data sparsity issue, the randomization stratification factor will be removed from the imputation model. The primary endpoint data from the 30 datasets will then be separately analyzed using the method described in Section 9.3.1. The results will be combined using SAS PROC MIANALYZE to generate the final inference.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the status of each live female adult worm as without *Wolbachia*, assessed by immunohistology of nodules collected after nodulectomy at Month 6.

9.3.2 Main Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint will be compared between the following pairs of treatment arms for the PP population in Part 1:

- For proof of concept: (1) A vs. E, (2) B vs. E, (3) C vs. E, (4) D vs. E;
- For satisfying the combination rule: if Arm C is to advance to Study B18-894/DNDi-TYL-01 Part 2, then (1) C vs. A, (2) C vs. E; if Arm D is to advance to Part 2 but Arm C is not, then: (1) D vs. A, (2) D vs. E.

The comparisons will be conducted using contrasts from an alternating logistic regression model[3] that includes all the five treatment arms as factors. The alternating logistic regression will account for within-subject association of the worm-level endpoint by estimating the pairwise log odds ratio (different than the odds ratio of the primary estimand) of a worm's *Wolbachia* status in relation to another worm's *Wolbachia* status within each subject. In this regression model, the within-subject association is estimated with one parameter. That is, the pairwise log odds ratios used to account for the within-subject association are assumed as equal for all pairs of worms within a subject, and the same log odds ratios are assumed for all subjects in the same treatment arm. However, different log odds ratios/parameters are assumed in different treatment arms, allowing for arm-specific within-subject associations. If the model does not converge, the within-subject associations for the five treatment arms will be assumed as the same. If the model still does not converge, a generalized linear mixed model will be used instead of the alternating logistic regression model. The mixed model will assume the framework of a logistic regression using a random intercept for each subject to account for the within-subject association of the worm-level endpoint. The variance of the random intercepts will be assumed as different for the five treatment arms.

Odds ratios with p-values and 95% confidence intervals for each of the pairwise comparisons will be reported. In addition, the percentages of live female adult worms without *Wolbachia* out of all live female adult worms from subjects in the PP population will also be summarized by treatment arm with 95% Wilson's score confidence intervals for all the percentages. The numerator and denominator of the percentage will be a sum across all subjects in a treatment arm. The rules of Section 9.2 for imputing missing data in the PP population worms will be applied; any worms that still have missing *Wolbachia* status after that will be excluded from both the numerator and denominator.

The attributes of the estimands corresponding to the primary efficacy endpoint are summarized in Table 1.

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint

Estimand Label	Attributes of the Estimand				
	Treatment	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Proof of concept	Arm A: ABBV-4083 for 7 days Arm B: ABBV-4083 for 14 days Arm C: ABBV-4083 for 7 days + albendazole for 7 days Arm D: ABBV-4083 for 7 days + albendazole for 3 days Arm E: albendazole for 7 days	Status of depletion of *Wolbachia* in each live female adult worm, evaluated using nodules collected at Month 6	PP population: all subjects who completed treatment and did not take prohibited medication, who had Month 6 nodulectomy with female worms	IE1: Subjects who did not complete treatment (6 out of 7 days for Arms A, C, E, 12 out of 14 days for Arm B, 6 out of 7 days of ABBV-4083 and all 3 days of albendazole for Arm D) will be excluded. IE2: Subjects who did not have Month 6 nodulectomy data will be excluded. IE3: Subjects who took prohibited medications will be excluded.	Odds ratio of *Wolbachia* depletion in live female adult worms in subjects taking active regimen vs. control regimen
Satisfying the combination rule	Arm A Arm C (or D depending on Part 2 regimens) Arm E	Same as above	Same as above	Same as above	Odds ratio of *Wolbachia* depletion in live female adult worms in subjects taking the combination regimen vs. the single drug regimens

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

As supplementary analyses of the primary endpoint, the same analyses listed in Section 9.3.2 will be repeated for the ITT population following the imputation rules for the missing *Wolbachia* depletion results at Month 6 (Section 9.2).

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Key Secondary Efficacy Endpoints and Analyses

There is no key secondary efficacy endpoint in Study B18-894/DNDi-TYL-01 Part 1.

9.4.2 Supportive Secondary Efficacy Endpoints and Analyses

The supportive secondary efficacy endpoints include the following:

- Proportion of live female adult worms with only degenerated embryos out of all live female adult worms with either normal embryos or only degenerated embryos in the uterus per subject at Month 6;
- Proportion of live female adult worms out of all female adult worms per subject at Month 6;
- The status of each subject as without microfilariae in nodular tissue at Month 6;
- The status of each subject as without skin microfilariae 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 nodule that contains at least 1 live female adult worm as without *Wolbachia*, as assessed by PCR, at Month 6.

All supportive secondary efficacy endpoints will be analyzed in the ITT population using observed data. All summaries will be produced by treatment arm.

The proportion of live female adult worms out of all female adult worms in each subject at Month 6 will be calculated as a percentage per subject. The proportion of live female

adult worms with only degenerated embryos out of all live female adult worms with either normal embryos or only degenerated embryos in the uterus in each subject at Month 6 will also be calculated as a percentage per subject, excluding from the denominator any worm with an empty uterus, with oocytes only, or not evaluable. Subjects with no worm for the denominator will be excluded from this summary. The percentage per subject will be summarized with descriptive statistics (number of subjects, mean and standard deviation, median, Q1, Q3, minimum, and maximum). P-values for the pairwise comparison of each of Arms A, B, C, D with Arm E will be provided using the Mann Whitney U test for the percentage per subject.

The status of each subject as without microfilariae in nodular tissue at Month 6 will be summarized as the percentage of subjects without microfilariae in nodular tissue at Month 6. The status of each subject as without skin microfilariae or not at Months 3 and 6 will be summarized in the same way. P-values for the pairwise comparison of each of Arms A, B, C, D with Arm E will be provided using the chi-square test for the binary response per subject.

The status of each nodule that contains at least 1 live adult female worm as without *Wolbachia*, as assessed by PCR at Month 6 will be summarized as the percentage of nodules without *Wolbachia* out of all nodules. The numerator and denominator of the percentage will be a sum across all subjects in a treatment arm. For the calculation of the percentages, nodules that do not contain live adult worms will be excluded from both the numerator and denominator. P-values for the pairwise comparison of each of Arms A, B, C, D with Arm E will be provided using the alternating logistic regression as detailed in Section 9.3.2 for the binary response per nodule clustered by subject.

The reduction in skin microfilarial density at Months 3 and 6 compared to baseline will be a mean change across all subjects summarized with descriptive statistics (number of subjects, mean and standard deviation, median, Q1, Q3, minimum, and maximum). The mean skin microfilarial density at baseline, Month 3 and 6 will also be summarized. P-values for the pairwise comparison of each of Arms A, B, C, D with Arm E will be provided using the Mann Whitney U test for the change from baseline in skin microfilarial

density per subject. The skin microfilarial density of each subject at a given time point will be collected as the final mean density of all the available skin snips. A supplementary analysis will be performed for this endpoint including only the final mean density values from ≥ 2 skin snips.

9.5 Additional Efficacy Analyses

The additional efficacy endpoints include the following:

- The status of each subject as without *Wolbachia* in skin microfilariae or not, as assessed by PCR, at baseline (screening), Month 3, Month 6, and end of study follow-up (including premature discontinuation);
- The decline in number of *Wolbachia* (assessed by PCR) in skin microfilariae per subject at Month 3, Month 6 and end of study follow-up (including premature discontinuation) compared to baseline;
- The microfilaria levels in the cornea and anterior chamber per subject, at baseline (screening), Day 13, Month 3, Month 6, and end of study follow-up (including premature discontinuation);
- the presence, severity and clinical evolution of onchocerciasis ocular disease and onchocerciasis skin disease in each subject at baseline (screening), Day 13, Month 3, Month 6, and end of study follow-up (including premature discontinuation).

All additional efficacy endpoints will be analyzed in the ITT population using data as observed. All analyses will be descriptive summaries and will be produced by treatment arm. No statistical method will be used for any pairwise comparison between arms.

The status of each subject as without *Wolbachia* in skin microfilariae or not, as assessed by PCR, will be summarized as the percentage of subjects without *Wolbachia* in skin microfilariae for each time point.

The decline in number of *Wolbachia* (assessed by ratio of PCR copy number of *Wolbachia* signal to PCR copy number of worm signal, FtsZ/Actin ratio) in skin

microfilariae per subject will be a mean change from baseline across all subjects summarized for each post-baseline time point with descriptive statistics (number of subjects, mean and standard deviation, median, Q1, Q3, minimum, and maximum). The mean number of *Wolbachia* in skin microfilariae at baseline and post-baseline time points will also be summarized.

The microfilaria levels (motile, non-motile, and total) in the cornea and anterior chamber will both be summarized as continuous variables using descriptive statistics (number of subjects, mean and standard deviation, median, Q1, Q3, minimum and maximum) for each time point. The values from the left and the right eye will be summarized separately.

Onchocerciasis ocular disease at each time point will first be summarized as the percentage of subjects with "abnormal" results from the following examinations: frequency doubling technology perimetry; pupils, extraocular movement and eyelids (pen torch); intraocular pressure (Goldman tonometer); anterior segment (slit lamp); iris anterior chamber examination; lens/cataract examination; posterior segment (slit lamp); fundus photography; visual acuity for distance; and ocular symptoms.

Then for each of the following outcomes, the percentage of subjects will be summarized for each clinical grade at each time point: ocular itching, watering eyes, ocular pain, photophobia, eye redness, blurred vision, night blindness, conjunctivitis, limbitis, punctate opacities, sclerosing keratitis, phlyctenule-like kerato-conjunctival lesions, anterior uveitis (number of cell/field and flare), cataract, glaucoma, optic nerve edema, optic nerve atrophy, posterior uveitis, chorioretinal atrophy, eyelid, chemosis, and visual field defect. The change of clinical grade from baseline will be summarized as improvement, no change, or worsening. The outcomes of the right eye and the left eye will be combined by using the higher grade of the two. The percentage of subjects will be summarized for each change category at each post-baseline time point, as well as the last post-baseline value. The clinical grading collected by the eCRF all starts from 1 for subjects with the outcome at a visit, but for the sake of analyses, grade 0 will be applied to subjects without the outcome at that visit. Outcomes with a binary evaluation (normal/abnormal, no/yes) will

be analyzed as grade 0 and 1. If the result of a particular examination is normal, all outcomes in that examination will also be normal (grade 0).

For the outcome of visual acuity (uncorrected, corrected, and color vision), continuous measures will be collected. The mean change from baseline at each post-baseline time point will be summarized across all subjects with descriptive statistics (number of subjects, mean and standard deviation, median, Q1, Q3, minimum and maximum). The mean at baseline and each post-baseline time point will also be summarized. The values from the left and the right eye will be summarized separately.

Onchocerciasis skin disease at each time point will first be summarized as the percentage of subjects with each of the symptoms collected on the skin examination eCRF form, based on the "present/absent" question. Then for each of the symptoms, the percentage of subjects will be summarized for each clinical grade at each time point. The change of clinical grade from baseline will be summarized as improvement, no change, or worsening. The percentage of subjects will be summarized for each change category at each post-baseline time point, as well as the last post-baseline value. When applicable, "Sum (clinical grading)" on the eCRF form will be used as the clinical grade. Otherwise, the single grading variable will be used and will be interpreted as an ordinal scale as applicable. For each symptom, the clinical grade will start from 1, but for the sake of analyses, grade 0 will be applied to subjects without the symptom.

9.6 Efficacy Subgroup Analyses

The percentages of live female adult worms without *Wolbachia* out of all live female adult worms from subjects in the PP population will be summarized by treatment arm for each category of the following subgroup variables, after applying the rules of Section 9.2 for missing data. 95% Wilson's score confidence intervals will be provided for all the percentages if the denominator is ≥ 10. The rules of Section 9.2 for imputing missing data in the PP population worms will be applied; any worms that still have missing *Wolbachia* status after that will be excluded from both the numerator and denominator. The subgroup variables include:

- Operable sites with onchocercomata (0, 1, or > 1),
- Baseline skin microfilarial density (≤ 5 or > 5 mf/mg),
- Number of previous ivermectin rounds (0, 1, or > 1)
- Time since the last ivermectin administration (≤ 1 year or > 1 year)
- District of residence (Kimpese, Masa, Masi-Manimba, Moanza, Nsonampangu, Pay Kongila, or Other)

The different treatment effects across these subgroup variables will be further explored using the alternating logistic regression model detailed in Section 9.3.2. The continuous values of the subgroup variables will be used except for district of residence. Each subgroup variable will be added separately to the model as a factor in addition to the treatment arms. Then, the interaction term of the subgroup variable with the treatment arms will be included in addition to the main effect term and analyzed in a separate model to examine the effect of the subgroup variables on treatment efficacy.

10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Safety population in Part 1. If any of Arms A B C, D was closed during the study and any of Arms F, G, H, I was opened, all individual treatment arms will be included in the safety analyses. All safety summaries will be presented by treatment arm, as well as for all subjects taking ABBV-4083 (i.e., combining Arms A, B, C, D, as well as, F, G, H, I, if applicable). For the safety analyses, a subject's treatment arm will be determined based on the treatment arm assigned at randomization.

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study

report. Specific PTs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same PT occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset date that is after the first dose of study drug and no more than 30 days after the last dose. Events with the same onset date as the study drug start date are assumed to be treatment-emergent. All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC. The number and percentage of subjects experiencing treatment-emergent AEs will be summarized.

10.2.2 Adverse Event Overview

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- Any treatment-emergent AE;
- Any treatment-emergent AE related to study drug (ABBV-4083, albendazole, ABBV-4083 and/or albendazole, and ABBV-4083 and albendazole) according to the investigator;
- Any Grade 3 or higher treatment-emergent AE (or if an AE is not graded as such, using maximum severity instead and including AEs that are severe, life-threatening, or led to death);
- Any serious treatment-emergent AE;
- Any serious treatment-emergent AE related to study drug (ABBV-4083, albendazole, ABBV-4083 and/or albendazole, and ABBV-4083 and albendazole) according to the investigator;
- Any treatment-emergent AE leading to discontinuation of study drug (ABBV-4083, albendazole, ABBV-4083 and/or albendazole, and ABBV-4083 and albendazole);

- Any treatment-emergent AE leading to death;
- All deaths during the study, deaths occurring prior to or at 30 days after the last dose, and deaths occurring > 30 days after the last dose.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent AEs will be summarized by SOC and PT; by maximum relationship to study drug as assessed by the investigator and SOC and PT; by maximum grade/severity and SOC and PT; and by subject number and SOC and PT. Specific PTs will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same PT occurs multiple times within a subject, the highest grade/severity and level of relationship to investigational product will be reported. The relationship to study drug will be collected as "definitely related," "probably related," "possibly related," "probably not related" and "not related," but it will be summarized as "related" (combining "definitely related," "probably related," "possibly related") and "not related" (combining "probably not related" and "not related"). Summaries of treatment-emergent AEs by maximum relationship to study drug, SOC and PT will be performed separately by relationship to ABBV-4083, relationship to albendazole, relationship to ABBV-4083 and albendazole, and relationship to ABBV-4083 and/or albendazole.

For the summary of treatment-emergent AEs, the maximum severity is determined by using reported per CRF severity as mild, moderate, severe, life-threatening, and death; CTCAE grades 1-5 as categories mild, moderate, severe, life-threatening, and death; or Vaccine Trial grades 1-4 as categories mild, moderate, severe, and life-threatening.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency among all subjects taking ABBV-4083.

10.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

Treatment-emergent SAEs (including deaths) and AEs leading to study drug discontinuation (ABBV-4083, albendazole, ABBV-4083 and albendazole, and

ABBV-4083 and/or albendazole) will be summarized by SOC and PT and in listing format. Listings of all SAEs and all deaths during the study will also be provided.

10.3 Analysis of Laboratory Data

Haematology variables to be summarized include: haematocrit, haemoglobin, red blood cells (RBC), white blood cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelets.

Chemistry variables to be summarized include: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glucose, creatinine, eGFR, blood urea nitrogen (BUN), total bilirubin, albumin, total protein, chloride, sodium, potassium and calcium.

Each laboratory variable will be summarized for all time points (Baseline, Day 3, Day 6, Day 13, Month 3, and end of study follow-up) with the number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for all laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment arm and difference between the active arms and the control arm (A, B, C, D vs. E) and between all active arms and the control arm (A – D vs. E) using separate ANOVA models.

Changes in chemistry and hematology laboratory parameters will be tabulated using shift tables, for laboratory parameters that have a normal range reported. Laboratory data values will be categorized as low, normal, or high based on the normal ranges of the laboratory used for each sample. Shift tables from baseline to the minimum and maximum values during the Treatment Period will be created. In these shift tables, the number and percentage of subjects with baseline values within or above the normal range (baseline high or normal) and a minimum value below the normal range (post-baseline low during treatment) and the number and percentage of subjects with baseline values within or

below the normal range (baseline low or normal) and a maximum value above the normal range (post-baseline high during treatment) will be summarized. Similar shift tables will be created for the shift from baseline to the final post-baseline value where the number and percentage of subjects with baseline values within or above the normal range (baseline high or normal) and the final post-baseline value below the normal range and the number and percentage of subjects with baseline values within or below the normal range (baseline low or normal) and the final post-baseline value above the normal range will be summarized.

The number and percentage of subjects with a maximum of Grade 3, a maximum of Grade 4, and a maximum of at least Grade 3 (CTCAE 5.0) for the laboratory parameters during treatment as defined in Appendix C will be summarized. The post-baseline value must be in a toxicity grade that is more extreme than the toxicity grade corresponding to the baseline value, if a baseline value is available, in order to be counted. A listing of all relevant laboratory parameters will be provided for each subject who had an increase to Grade 3 or higher.

The following criteria will be used to assess potential hepatotoxicity during treatment.

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- bilirubin > 1.5 × ULN, > 2 × ULN
- ALT and/or AST > 3 × ULN and bilirubin > 1.5 × ULN
- ALT and/or AST > 3 × ULN and bilirubin > 2 × ULN
- ALT > 3 × ULN and bilirubin > 1.5 × ULN
- ALT > 3 × ULN and bilirubin > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN

The number and percentage of subjects with laboratory values meeting the above criteria during treatment will be summarized. Listing of ALT, AST, total bilirubin, and alkaline phosphatase values will be provided for each subject who met one or more of the criteria defined above.

An Evaluation of Drug Induced Serious Hepatotoxicity (eDISH) plot of the maximum post-baseline ALT value (as a multiple of the ULN) versus the maximum post-baseline bilirubin value (as a multiple of the ULN) during treatment, not necessarily concurrent, will also be utilized to assess for potential hepatotoxicity. A similar plot will be produced for AST versus bilirubin.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, heart rate, resting respiratory rate and temperature will be summarized.

Each vital sign variable will be summarized for all time points (Baseline, Day 3, Day 6, Day 13, Month 3, and end of study follow-up) with the number of non-missing observations, mean and standard deviation, median, Q1, Q3, minimum, and maximum. Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard error, and 95% confidence interval will be presented for the mean change from baseline within each treatment group and difference between treatment arms (A, B, C, D vs. E) and between all active arms and the control arm (A – D vs. E) using separate ANOVA models.

Vital signs variables will be evaluated based on potentially clinically important (PCI) criteria (Appendix C) using all post-baseline values. For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

10.5 Other Safety Analyses

ECG findings will be summarized for all time points (Baseline, Day 3, Day 6, Day 13, and end of study follow-up) using the investigator interpretation. The summaries will include the number and percentage of patients in the following categories:

- Normal
- Abnormal – Not Clinically Significant
- Abnormal – Clinically Significant

Counts will be provided for the category "Interpretation not possible."

11.0 Interim Analyses

No interim analysis is planned for Study B18-894/DNDi-TYL-01 Part 1.

11.1 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be established by the Sponsor in accordance with ICH guidelines. The DSMB will be composed of a minimum of three members, including at least one medically qualified disease expert and a statistician, in accordance with any requirements specified by the regulatory authorities. The composition, roles, and responsibilities of the DSMB will be described in detail in a separate DSMB charter.

During the study, the DSMB will review reports 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 (only drug concentration data), concomitant treatments, as well as ad-hoc requests if deemed necessary by the Sponsor and in line with the DSMB charter.

The DSMB will also review and evaluate, at intervals and as defined in the DSMB charter, the progress, scientific validity, data integrity, and the safety of the clinical trial, and make recommendations to the Sponsor about whether to continue, modify or terminate the trial. The DSMB may also 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.

In addition, 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 a separate SRC Charter.

Once at least 15 subjects have been treated in each of the five arms, the SRC will review safety results separately for each arm every 2 weeks and evaluate causality. If > 10% of the subjects in any arm meet any of the toxicity criteria, the SRC will inform the DSMB. The DSMB will review the reports and make non-binding recommendations regarding halting enrolment into Arms A, B, C or D and opening enrolment in appropriate arms with the lower dose of ABBV-4083.

Both the Sponsor and the DSMB will review the final unblinded analyses of Study B18-894/DNDi-TYL-01 Part 1. The DSMB will provide a non-binding recommendation to the Sponsor about whether to proceed to Part 2 and with which dose regimens.

12.0 Overall Type-I Error Control

Since Study B18-894/DNDi-TYL-01 Part 1 is for proof of concept, no multiplicity adjustment for alpha spending will be used.

13.0 Version History

Table 2. SAP Version History Summary

Version	Date	Summary
1.0	02 Nov 2021	Original version
2.0	24 Mar 2023	• Section 1.0 Noted that analyses inconsistent with the protocol are noted in Section 13.0. • Section 2.3 Administrative clarification of randomization was made.

Version	Date	Summary
		• Section 3.2 and Section 9.4.2 Secondary endpoint of status of each live female adult worm as without Wolbachia assessed by PCR at Month 6 has been changed to status of each nodule containing at least one live female adult worm as without Wolbachia assessed by PCR at Month 6 due to a change in PCR data availability. • Section 3.4 For safety endpoints, removed physical, skin, and ophthalmological examination findings since they are summarized as the secondary efficacy endpoints. • Section 3.4 For safety endpoints, removed urine analysis because only abnormal results are collected. • Section 4.0 and Section 10.1 Updated safety analysis arms to be determined by the subject's randomized arm to align with treatment regimens under study. • Section 5.0 Subject disposition summary for completed protocol-specified treatment, prematurely discontinued study drug, reason for discontinuation of study drug, interruption of study drug, and reason for interruption of study drug were clarified to include summaries by study drug. • Section 6.0 Study drug duration categorical summary was updated to add the category of "> 14 days." • Q1, Q3 were added to all numerical summaries that included calculation of the median. • Section 7.1 and Section 9.6 For demographics and baseline characteristics, categories for number of operable sites with onchocercomata, number of palpated nodules, and number of previous ivermectin rounds were updated to be 0, 1, >1. Also, number of years resident in endemic area was added, and for summary of symptoms of onchocerciasis disease, "other" category was removed. • Section 7.3 Summaries of prior and concomitant procedures were removed because they are collected as text fields. Anthelmintic medications taken prior to the start of study drug were removed from the summary of concomitant medications because by definition these medications were only taken prior to start of study drug. • Section 8.0 and Section 9.2 Clarified the conditions which lead to data imputation. • Section 9.1 Clarified that no adjustment for multiple comparisons would be made.

Version	Date	Summary
		• Section 9.5 Clarified that the decline in number of *Wolbachia*, as assessed by PCR, would be assessed using the ratio of PCR copy number of *Wolbachia* signal to PCR copy number of worm signal. • Section 9.5 For ophthalmological exam outcomes, added blurred vision and night blindness to summary of clinical grade and clarified that anterior uveitis would have separate grades for number of cell/field and flare). For summaries of change from baseline in ocular and skin exam, summary category of "similarity" was changed to "no change." • Section 10.2.2, Section 10.2.3, and Section 10.2.4 Clarified that summaries of treatment-emergent AEs based on relationship to study drug and of treatment-emergent AEs leading to discontinuation of study drug would be performed with study drug defined in 4 ways: ABBV-4083, albendazole, ABBV-4083 and/or albendazole, and ABBV-4083 and albendazole. The description of the summary of all deaths was clarified to include time periods. • Section 10.2.4 Added listings of all SAEs and all deaths. • Section 10.3 Deleted statement about including laboratory testing due to an SAE because SAE-related laboratory assessments are not collected in a format that can be summarized. Removed summary of creatinine clearance and added eGFR because eGFR is collected in the study and is more applicable to the study population. Removed summary of urinalysis data because only abnormal results are collected. Clarified that changes from baseline would be analyzed using ANOVA models. Provided more detail about the analyses related to normal range shift for laboratory parameters. Added separate summaries for a maximum of Grade 3 and a maximum of Grade 4 for graded laboratory parameters. Added an eDISH plot for AST versus bilirubin. • Section 10.4 Clarified that changes from baseline would be analyzed using ANOVA models. Clarified that evaluation of potentially clinically important criteria are to be assessed using all post-baseline values.

Version	Date	Summary
		• Section 10.5 Deleted Month 3 visit summary because ECG data are not collected at Month 3. Clarified that only investigator interpretation of ECG would be summarized and that percentages would be calculated using only interpretable tests. • Appendix A Added the protocol deviation categories. • Appendix B Clarified that any subject taking a prohibited medication will be documented as a protocol deviation. • Appendix C Removed creatinine clearance from table and added eGFR because eGFR is collected in the study and is more applicable to the study population. Revised albumin criteria to use units of g/dL. Updated grade definitions for ALT, AST, ALP, and bilirubin to match CTCAE v5.

14.0 References

1. Albers A, Esum ME, Tendongfor N, et al. Retarded Onchocerca volvulus L1 to L3 larval development in the Simulium damnosum vector after anti-wolbachial treatment of the human host. Parasit Vectors. 2012;5:12.
2. Wu S, Crespi CM, Wong WK. Comparison of methods for estimating the intraclass correlation coefficient for binary responses in cancer prevention cluster randomized trials. Contemp Clin Trials. 2012;33(5):869-80.
3. Carey V, Zeger SL, Diggle PJ. Modelling Multivariate Binary Data with Alternating Logistic Regressions. Biometrika. 1993;80(3):517-26.
4. U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007.

15.0 SAP Approval

[redacted] AbbVie Statistics	Signature [redacted] Date (*DD-MMM-YYYY*): 24-Mar-2023
[redacted] AbbVie Statistics Director	Signature [redacted] Date (*DD-MMM-YYYY*): 24-Mar-2023
[redacted] AbbVie Statistical Programming	Signature [redacted] Date (*DD-MMM-YYYY*): 24-Mar-2023
[redacted] AbbVie Medical Director	Signature [redacted] Date (*DD-MMM-YYYY*): 24-Mar-2023
[redacted] AbbVie Group Medical Director	Signature: [redacted] Date (*DD-MMM-YYYY*): 24-Mar-2023
[redacted] DNDi Head of Filarial Program	Signature: [redacted] Date (*DD-MMM-YYYY*): 24-Mar-2023

[redacted] DNDi Medical Manager	Signature [redacted] Date (*DD-MMM-YYYY*): 27-Mar-2023
[redacted] DNDi Clinical Project Manager	Signature: [redacted] Date (*DD-MMM-YYYY*): 24-Mar-2023

Appendix A. Protocol Deviations

Protocol deviations include eligibility criteria violations, receipt of wrong treatment or incorrect dose of study treatment, development of withdrawal criteria without being withdrawn, use of prohibited concomitant medications, and Month 6 nodulectomy not performed. A listing of subjects with protocol deviations will be provided.

Appendix B. List of Prohibited Medications

The following medications are prohibited throughout the entire study because of their anti-filarial or anti-Wolbachia effects:

- ivermectin (excluding protocol-defined, post-study ivermectin mentioned in Section 2.2)
- moxidectin,
- doxycycline,
- minocycline,
- rifampicin,
- rifapentine.

The following medications are prohibited during the treatment period, up to 24 hours after the final dose.

- Any CYP3A and/or P-gp inhibitors or inducers, such as:
  - rifampicin,
  - phenytoin,
  - phenobarbital,
  - carbamazepine,
  - others known to interfere with the CYP3A and/or P-gp metabolic pathways (the US FDA tables of Substrates, Inhibitors and Inducers will be used as a reference, and included in the Study Operations Manual for reference).
- Dexamethasone is known to interact with albendazole and will also be prohibited during the treatment period, up to 24 hours after the final dose.

Any subject who takes a prohibited medication during the study will be documented via a protocol deviation, which will be used to determine eligibility for the per-protocol population.

Appendix C. Potentially Clinically Important Criteria for Safety Endpoints

Table C-1. Definitions of Toxicity Grades 1, 2, 3, and 4 for Laboratory Values

Test	Grade 1	Grade 2	Grade 3	Grade 4
ALT*	> ULN – 3 × ULN if baseline was normal or missing; 1.5 – 3 x baseline if baseline was abnormal	> 3 – 5 × ULN*	> 5 – 20 × ULN*	> 20 × ULN*
AST*	> ULN – 3 × ULN if baseline was normal or missing; 1.5 – 3 x baseline if baseline was abnormal	> 3 – 5 × ULN*	> 5 – 20 × ULN*	> 20 × ULN*
ALP*	> ULN – 2.5 × ULN if baseline was normal or missing; 2 – 2.5 x baseline if baseline was abnormal	> 2.5 – 5 × ULN*	> 5 – 20 × ULN*	> 20 × ULN*
Bilirubin*	> ULN – 1.5 × ULN if baseline was normal or missing; 1- 1.5 x baseline if baseline was abnormal	> 1.5 – 3 × ULN*	> 3 – 10 × ULN*	> 10 × ULN*
Haemoglobin (female)+	11.0 – 12.0 g/dL	9.5 – 10.9 g/dL	8.0 – 9.4 g/dL	< 8.0 g/dL
Haemoglobin (male)+	12.5 – 13.5 g/dL	10.5 – 12.4 g/dL	8.5 – 10.4 g/dL	< 8.5 g/dL
White blood cells	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Platelets	< LLN – 75.0 × 10^9/L	< 75.0 – 50.0 × 10^9/L	< 50.0 – 25.0 × 10^9/L	< 25.0 × 10^9/L
Glucose (decreased)	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L
Creatinine	> ULN – 1.5 × ULN	> 1.5 – 3 × ULN	> 3 – 6 × ULN	> 6 × ULN
eGFR	< 90 – 60 mL/min/1.73m^2	< 60 – 30 mL/min/1.73m^2	< 30 – 15 mL/min/1.73m^2	< 15 mL/min/1.73m^2
Albumin	< LLN – 3 g/dL	< 3 – 2 g/dL	< 2 g/dL	--

* ULN used as reference if baseline was normal or missing; if baseline was abnormal (> ULN), baseline should be used as reference, for example, > ULN – 3 × ULN should be changed to > baseline – 3 × baseline if baseline was abnormal, according to CTCAE v5.

\+ Haemoglobin values are taken from the Vaccine Trial Grading Scale 2007.[4]

Table C-2. Criteria for Potentially Clinically Important Vital Sign Values

Test/Measurement	Low	High
Systolic Blood Pressure	≤ 90 mmHg and a decrease of ≥ 20 mmHg from baseline	≥ 180 mmHg and an increase of ≥ 20 mmHg from baseline
Diastolic Blood Pressure	≤ 50 mmHg and a decrease of ≥ 15 mmHg from baseline	≥ 105 mmHg and an increase of ≥ 15 mmHg from baseline
Heart Rate	≤ 50 bpm and a decrease of ≥ 15 bpm from baseline	≥ 120 bpm and an increase of ≥ 15 bpm from baseline
Body Temperature		> 38.3°C and an increase of ≥ 1.1°C from baseline