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Clinical Development

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A Phase IV, multi-center, open-label study to determine the safety, tolerability and clinical outcomes following oral administration of EGATEN™ (Triclabendazole) in patients (6 years of age or older) with fascioliasis

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interst
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
bid	bis in diem/twice a day
CRS	Case Retrieval Sheet
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
FAS	Full Analysis Set
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
MedDRA	Medical Dictionary for Drug Regulatory Affairs
QTcF	QT Interval Corrected by the Fridericia Correction Formula
SAF	Safety Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
TBL	Total Bilirubin
TFLs	Tables, Figures, Listings
TSR	Rapid Sedimentation Technique
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis which is planned in the protocol. The study is an open label single-arm Post Marketing Commitment (PMC 3556-2) to the Food and Drug Administration (FDA) and will evaluate safety and tolerability along with clinical outcomes of Egaten when administered as per FDA approved dosing regimen of 2 doses of 10 mg/kg given approximately 12 hours apart in approximately 300 Fascioliasis patients (≥ 6 years of age). Annual interim reports are planned for submission based on the US FDA PMC milestones and will provide safety data as well as clinical and parasitological cure outcomes. The final clinical study report (CSR) will be prepared after the final database lock (DBL). This single SAP will be used for the analysis of data collected at each interim assessment and at the end of the study.

1.1 Study design

This is a multi-center, multi-country, open label, non-comparative, single arm study in approximately 300 adult and pediatric subjects (≥ 6 years of age) with fascioliasis. Enrolled subjects will receive two doses of 10 mg/kg of Egaten given approximately 12 hours apart. Subjects will preferentially be treated and followed up on an outpatient basis. Subjects with acute/symptomatic disease or requiring post-dose ECG monitoring could be hospitalized at investigator's discretion.

After screening and post treatment, at Day 3 and Day 6 the subjects will be followed for safety and tolerability. These visits are primarily for safety follow up and may be telephonic or home visit by qualified personnel or onsite visits based on the investigator's discretion. During visits Day 10, Day 30, Day 60 and Day 90 post-treatment, the subjects will be followed for safety, tolerability and efficacy.

On Day 15, Day 45 and Day 75, telephonic follow-up (primarily for safety) will be conducted.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	Endpoint(s) for primary objective(s)
To evaluate safety and tolerability of Egaten administered as two 10 mg/kg doses given approximately 12 hours apart in subjects with fascioliasis.	Safety/tolerability assessments (incidence of serious adverse events (SAEs), adverse events (AEs), and laboratory assessments).
Secondary objective(s)	Endpoint(s) for secondary objective(s)
To evaluate clinical response in acute and chronic Fascioliasis subjects on Day 10	At Day 10, improvement or resolution of baseline signs and symptoms
To evaluate clinical cure rate in Acute Fascioliasis subjects on Day 30, Day 60 and Day 90.	At Day 30, Day 60 and Day 90, proportion of subjects with: • Resolution of baseline signs and symptoms. • Improvement in baseline lab parameters. • Improvement in baseline ultrasound findings.

Objective(s)	Endpoint(s)
To evaluate parasitological cure rate of chronic fascioliasis subjects at Day 10, Day 30, Day 60 and Day 90.	Proportion of subjects with absence of fasciola eggs confirmed by stool examination at Day 10, Day 30, Day 60 and Day 90.
To evaluate clinical cure rate of chronic fascioliasis subjects at Day 30, Day 60 and Day 90.	At Day 30, Day 60 and Day 90 proportion of subjects with : • Resolution of baseline signs and symptoms. • Improvement in baseline lab parameters. • Improvement in baseline ultrasound findings.

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Datamap on behalf of Novartis for the annual interim assessment reporting and after final DBL using latest version of SAS available with Datamap according to the data analysis presented in section 12 of the study protocol which will also be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

At the end of the trial, full statistical analyses will be performed. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The outline of reports for annual interim assessment are listed in Table 2-6 and will be detailed in the CSR TFL shells. A separate SAP and TFL shell for annual interim assessment reporting is not needed since the statistical methods for annual interim assessment reporting are same as those in this SAP.

Information on visit windows, imputation rules and the methods of efficacy and safety analyses is given in the sections to follow and details will be provided, as applicable, in Appendix 16.1.9 of the CSR. This SAP covers the methods for both planned annual interim assessment reporting and the final analysis.

Unless otherwise stated, summary tables/figures/listings will be on all patients included in the population under consideration.

Categorical data will be presented as frequencies and percentages. For continuous data, n, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Statistical analysis may be performed on subgroups not mentioned in this SAP for Exploratory purposes.

2.1.1 General definitions

Study treatment: Egaten is the interventional treatment. It is referred to as study treatment in the document.

Summary results will be presented by treatment group. The following abbreviated treatment group label will be used as the column header in the CSR outputs:

- EGATEN 10 mg BID

Baseline: The last measurement made prior to and including administration of the first dose of study treatment. Note this may include measurements taken during pre-screeening/Screening window (e.g. demography, lab, Physical examination, ECG, vital signs, etc.). If there is no baseline value for subjects for stool test data, baseline definition will be enlarged to consider also assessments done at treatment start date + 1 day as baseline. If a patient did not receive any dose of study treatment then the enrollment date will be used as the date of first dose of study treatment for study day calculations.

Study day: Study day will be calculated with respect to the first dose of study treatment. The first day of administration of study treatment (first dose) is defined as Day 1. Day -1 will be the day before Day 1. Day 0 does not exist.

For assessments collected on or after Day 1, study day = date of assessment – date of first dose of study treatment + 1.

For assessments collected prior to Day 1, study day = date of assessment - date of first dose of study treatment.

Type of fascioliasis: Type of fascioliasis (acute or chronic) will be determined by type of fascioliasis as assessed by PI on the CRF. If type of fascioliasis is not available on the CRF, a subject will be considered as acute, if there are no eggs present in stool and a subject will be considered as chronic, if there are any eggs present in stool. Patients for whom the type of fascioliasis could not be determined by the PI, and stool sample assessment was missing at baseline, are considered as ‘Undetermined’ for analysis based on ‘Type of fascioliasis’.

Subjects who received rescue medication during the study or who have no resolution of baseline signs and symptoms or no improvement from baseline lab parameters or ultrasound findings of Fascioliasis or presence of Fasciola eggs in feces on end of study visit (D90 visit) would be considered treatment failures and they will be managed as per local treatment guidelines. All patients will be followed up for the safety evaluation until Day 90 of the study.

2.1.1.1 Clinical cure

a. For Day 10 clinical response will be evaluated as below
    1. Improvement/Resolution of baseline signs and symptoms,
b. Days 30, 60 and 90 clinical cure will be evaluated as below
    1. Resolution of baseline signs and symptoms, and
    2. Improvement in baseline ultrasound findings, and
    3. Improvement in baseline laboratory parameters

The efficacy assessments performed in **Acute Fascioliasis** patients are listed in Table 2-1 and the efficacy assessments performed in **Chronic Fascioliasis** patients are listed in Table 2-2. For

Undetermined patients the components in Table 2-1 will be summarized separately without overall clinical cure as overall clinical cure is not defined in protocol for those undetermined.

Table 2-1 Efficacy Assessments for Acute Fascioliasis and Undetermined Patients

Clinical Endpoints	Assessments	Assessment Criteria
Clinical signs and symptoms	Fever Abdominal pain Gastrointestinal disturbances (loss of appetite, flatulence, nausea, diarrhea) Urticaria	Resolution of sign and symptoms present at baseline
Ultrasonography	Abdomen – for hepatic lesions and/or biliary tract blockage caused by Fasciola worm(s).	Improvement in ultrasound findings based on an assessment by a qualified radiologist
Hematology	Eosinophil count	≥ 50% reduction from baseline value or reaching normal range if baseline value was above normal range

Table 2-2 Efficacy Assessments for Chronic Fascioliasis patients

Clinical Endpoints	Assessments	Assessment Criteria
Clinical signs and symptoms	Fever Abdominal pain Gastrointestinal disturbances (loss of appetite, flatulence, nausea, diarrhea) Urticaria Ascites Jaundice Hepatomegaly Anemia	Resolution of sign and symptoms present at baseline
Ultrasonography	Abdomen – for hepatic lesions and/or biliary tract blockage caused by Fasciola worm(s).	Improvement in ultrasound findings based on an assessment by a qualified radiologist
Hematology and biochemistry	Hemoglobin	≥1 g/dL increase from baseline value or reaching normal range if baseline value was below normal range
	Eosinophil count	≥ 50% reduction from baseline value or reaching normal range if baseline value was above normal range
	Liver function test (ALT, AST, ALP, Bilirubin (Total, Direct and Indirect))	≥1 grade improvement from baseline or reaching normal range for each test if baseline value was above normal range
	Erythrocyte sedimentation rate (ESR)	≥ 50% reduction from baseline value or reaching normal range if baseline value was above normal range

2.1.1.2 Parasitologic cure

Parasitologic cure will be evaluated in chronic Fascioliasis (defined as presence of eggs in stool at baseline) subjects only. It is defined as absence of Fasciola eggs in feces on Day 10, Day 30, Day 60 and Day 90 confirmed by stool examination. In order to ensure correct detection of Fasciola eggs in feces, TSR (Rapid Sedimentation Technique, Lumbreras method) may be repeated to confirm a parasitological cure at each of the visits (Visits corresponding to Day 10, Day 30, Day 60, and Day 90). If the TSR stool test is positive on a particular day, assessment for subsequent sample need not be conducted. Egg count will be conducted using Kato-Katz test. Details of TSR (Lumbreras method) and Kato-Katz test is detailed in Protocol under Section 16.2: Stool assessments.

2.1.1.3 Definition for treatment failures

For acute/chronic patients, treatment failures for clinical cure will be defined as subjects:

1. Who received rescue medication during the study or
2. With no resolution of baseline signs and symptoms or no improvement from baseline lab parameters or ultrasound findings of Fascioliasis or presence of Fasciola eggs in feces on end of study visit (Day 90 visit);

Subjects assessed as clinical or parasitological failure on any of the visits will be administered rescue therapy (SoC as per the local treatment guidelines) and will be considered treatment failure for all the subsequent efficacy assessments.

Subjects who have received rescue medication at any point during the study period will be carried forward as treatment failures and will be followed up for safety till end of the study.

2.2 Analysis sets

Full analysis set (FAS) : FAS will be comprised of all patients who are enrolled in the study.

Safety set (SAF set) : Safety set includes all FAS patients who took at least one dose of study drug during the treatment period.

Since this study is not randomized, enrollment in the study starts with the intake of any dose of study medication.

2.2.1 Subgroup of interest

The following subgroups will be used for descriptive summary of the selected efficacy and safety analyses. The details will be provided in the corresponding sections.

- Sex (male vs female)
- Age group (6 - <12, 12 - <18, 18 - <65, >=65)
- Race

Subgroups will be presented separately for acute and chronic fascioliasis for efficacy parameters.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Medical History

Any condition entered on the *Relevant medical history / current medical conditions* CRF will be coded using the MedDRA dictionary. They will be summarized by primary system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. A separate summary will also be provided on medical conditions that were active at the time of screening.

Relevant medical history / current medical conditions will be listed.Medical conditions that are identified after informed consent has been signed but before the first dose of study medication is administered may be collected in the adverse event panel and will not be summarized with medical history but listed together will all other adverse events and flagged accordingly.

Unless otherwise specified, analyses will be based on the safety set.

2.3.2 Patient demographics and other baseline characteristics

Demographic data and baseline disease characteristics will be presented descriptively and tabulated (n, mean, standard deviation, median, minimum, and maximum for continuous variables; n and percent for categorical variables) overall and by acute, chronic and undetermined fascioliasis patients, using FAS set.

Following demographic variables will be summarized

- Age and age categories (6 - <12, 12 - <18, 18 - <65, >=65 yrs)
- Sex (male, female)
- Race
- Ethnicity
- Body height (cm) [measured at Screening visit]
- Weight(kg)
- BMI and BMI categories (<18.5, 18.5 to <25, 25 to <30, >=30) (kg/m^2)
- QTcF <450, 450 - <480, ≥480 msec

Following disease characteristics at baseline will be summarized

- Body temperature and the number and percentage of patients for categories (<37.5, 37.5 to <39, ≥39) (°C)
- Presence of eggs in feces detected by stool tests (TSR and Kato-Katz tests)
- Clinical symptoms and signs (fever, abdominal pain, gastrointestinal disturbances, urticaria, ascites, jaundice, hepatomegaly, anemia),
- laboratory evaluations
    - hemoglobin

- eosinophil count
- erythrocyte sedimentation rate (ESR)
- liver function test (ALT, AST, ALP, bilirubin (total, direct and indirect))

- Imaging – ultrasound to assess liver involvement
- Residence in endemic area

2.3.3 Patient disposition

The number of patients screened will be presented. In addition, the reasons for screen failures will be provided. This summary will be provided for all screened subjects.

The number and percentage of patients enrolled, who completed study and who discontinued study prematurely (including the reason for discontinuation) will be presented.

For each protocol deviation, the number and percentage of patients for whom the deviation applies will be tabulated.

FAS set will be used.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Number and percentage of subjects will be presented for the following categories:

- Subjects taking both doses
- Subjects taking only one dose
- Subjects taken no dose
- Subjects with study drug vomiting and dose replacement.
- Subjects taking more than 2 doses (other than replacement dose)

Note- If a patient vomited the original dose but did not vomit the replacement dose, the patient is considered as fully dosed.

Doses that were vomited will be excluded from the analyses even though patients who took at least one dose of study drug regardless of vomiting status are to be included in the Safety set.

In addition summary statistics) on actual doses taken will be presented.

Safety set will be used.

2.4.2 Prior, concomitant and post therapies

Prior and concomitant medications/non-drug therapies will be summarized in separate tables by treatment group.

Rescue medications will also be summarized by treatment group.

Prior medications/non-drug therapies are defined as drugs/non-drug therapies taken and stopped prior to first dose of study medication. Any medication/non-drug therapy given at least once between the day of first dose of study medication and the last day of study visit will be a concomitant medication/non-drug therapy, including those which were started pre-baseline and continued into the treatment period.

Prior and concomitant medications will be coded according to the latest version of WHO Drug Reference List dictionary which employs the ATC. The number and percentage of patients taking prior and concomitant medications will be summarized by ATC class and preferred term (PT).

Prior and concomitant medications will be listed.

Prior and concomitant non-drug therapies will be coded according to the latest MedDRA dictionary version. The number and percentage of patients taking prior and concomitant non-drug therapies will be summarized by system organ class (SOC) and PT.

Number and percentage of the patients receiving prohibited concomitant drugs will be summarized by category, ATC class and PT. Possible categories are Anthelmintics, CYP2C19 substrates requiring therapeutic drug monitoring and Medications with known risk of TdP. Details regarding prohibited drugs are mentioned in Section 5.2.

Safety set will be used.

2.5 Analysis of the primary objective

The primary objective is to evaluate safety and tolerability of Egaten administered as two 10 mg/kg doses given approximately 12 hours apart in subjects with fascioliasis

2.5.1 Primary endpoint

The primary objective is to evaluate the safety and tolerability of the study drug, including serious adverse events (SAEs), adverse events (AEs) and laboratory assessments.

All information obtained on adverse events will be displayed.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- By primary system organ class and preferred term.
- By primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

All laboratory data will be listed by subject and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by visit including shift tables using the low/normal/high.

2.5.2 Statistical hypothesis, model, and method of analysis

There is no formal statistical hypotheses testing for the primary endpoint. Statistical analyses will be mainly descriptive.

2.5.3 Handling of missing values/censoring/discontinuations

Missing or partially missing dates (year, month or day missing) will be handled using standard Novartis conventions, this is detailed in Section 5: Appendix.

2.5.4 Supportive analyses

No sensitivity analyses will be performed for the primary safety variables.

2.6 Analysis of the key secondary objective

There is no key secondary objective in this study.

2.7 Analysis of secondary efficacy objective(s)

Descriptive statistics for each secondary variable will be provided. For secondary endpoints, the proportion and confidence interval (CI) of subjects who are clinical cures for acute and chronic fascioliasis and/or parasitological cures for chronic fascioliasis as defined in Section 2.1.1 will be presented by visit.

2.7.1 Secondary endpoints

Summary of the clinical response (improvement or resolution of baseline signs and symptoms) in acute, chronic and undetermined fascioliasis patients on Day 10 will be provided.

Summary of the improvement of baseline signs and symptoms, Improvement in the lab parameters from baseline and Improvement in ultrasound findings from baseline on Day 30, 60 and 90 will presented separately for acute, undetermined fascioliasis (Table 2-1) and chronic fascioliasis(Table 2-2) patients.

The clinical cure rate that includes all the criteria combined will be evaluated for acute fascioliasis(Table 2-1) and chronic fascioliasis(Table 2-2) on Day 30, 60 and 90 .

- Resolution of baseline signs and symptoms for
    - Fever
    - Abdominal pain
    - Gastrointestinal disturbances (loss of appetite, flatulence, nausea, diarrhea)
    - Urticaria
    - Ascites (chronic)
    - Jaundice (chronic)
    - Hepatomegaly (chronic)
    - Anemia (chronic)

- Improvement in the following lab parameters from baseline
    - Hemoglobin (chronic)
    - Eosinophil count
    - Erythrocyte sedimentation rate (ESR) (chronic)
    - Liver function test (ALT, AST, ALP, Bilirubin (Total, Direct and Indirect)) (chronic)
- Improvement in below ultrasound findings from baseline
    - Abdomen – for hepatic lesions and/or biliary tract blockage caused by Fasciola worm(s).

The parasitological cure rate of chronic fascioliasis patients at Day 10, Day 30, Day 60 and Day 90 will also be presented separately for each of the following criteria

- Presence or absence of Fasciola eggs
- Descriptive summary statistics for the Fasciola egg count

Subjects without positive stool test at baseline are excluded from the analysis of parasitological cure rate.

The proportion of patients with clinical cure rate, resolution of baseline signs and symptoms, improvement of laboratory parameters, improvement in ultrasound findings for abdomen and parasitological cure at Day 90 will also be summarized by country for acute, chronic and undetermined fascioliasis patients. The combined criteria improvement of laboratory parameters is defined as all relevant (with respect to acute/chronic fascioliasis) laboratory parameters that were present at baseline improved at Day 90.

Handling of missing values/censoring/discontinuations

Patients who did not have any of the above listed efficacy assessment at the study baseline will not be included in the analysis of that particular resolution rate.

For any post baseline visit with missing efficacy assessment other than parasitological cure, no missing data imputation will be done. All patients who had protocol defined signs and symptoms or abnormal laboratory parameters, or ultrasound findings for abdomen at baseline will be included in the analysis. Additionally a row for patient missing the post baseline assessment will be presented by visit for each of the above efficacy assessments. For the imputation of parasitological cure at any post-baseline visit the imputation rule is outlined in section 5.1.2.

2.7.2 Statistical hypothesis, model, and method of analysis

There are no pre-specified hypotheses for secondary endpoints. Model and method of analysis are presented in the following sub-sections by topic.

2.7.2.1 Clinical cure rate

For Acute and Chronic fascioliasis and undetermined patients at Day 30, Day 60 and Day 90, the proportion and 95% confidence intervals will be provided using the Clopper-Pearson method for each of the parameters listed to check the Clinical cure.

In addition the proportion and 95% confidence intervals will also be provided by the following subgroups in Acute and Chronic fascioliasis patients

- Sex (male vs female)
- Age group (6 - <12, 12 - <18, 18 - <65, >=65 yrs)
- Race

Percentages/Proportions will be calculated based on the patients who showed this symptoms at baseline. For e.g. to calculate the percentage of patients with fever clearance only patients who had fever at baseline will be considered.

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2.7.2.2 Parasitological cure rate

For Parasitologic cure in chronic fascioliasis at Day 10, Day 30, Day 60 and Day 90, the proportion and 95% confidence intervals will be provided using the Pearson-Clopper method for each of the parameters listed to check the Clinical cure.

In addition, the proportion and 95% confidence intervals will also be provided by the following subgroups

- Sex (male vs female)
- Age group (6 - <12, 12 - <18, 18 - <65, >=65 yrs)
- Race

Parasitological cure is imputed according to the rules in section 5.1.2.

2.8 Safety analyses

All safety parameters will be analyzed based on the safety set.

2.8.1 Adverse events (AEs)

The number and percentage of patients with treatment emergent adverse events will be presented. The treatment emergent adverse events (events started on or after the first dose of study medication or events present prior to the first dose of study medication but increased in severity based on preferred term) will be summarized by MedDRA primary System Organ Class (SOC) and Preferred Term (PT).

Adverse events will be summarized by presenting, the number and percentage of patients having at least one AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity (CTC Toxicity grade) and for study treatment related AEs. If a patient reported more than one adverse event with the

same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable.

The MedDRA version used for reporting the adverse events will be described in a footnote.

The most common adverse events reported (≥ z % in any group for each preferred term in the table by SOC and PT) will be presented in the clinical study report by descending frequency according to its incidence in overall group starting from the most common event. Here the threshold value z is set to 3 (%) but it may be updated following review of the dry run outputs.

Separate summaries will be provided for death, serious adverse events, other significant adverse events leading to treatment discontinuation, adverse events leading to dose adjustment and adverse events suspected to be study drug related. Summaries will also be provided for adverse events within 15 days of drug administration, serious adverse events within 15 days of drug administration, and adverse events suspected to be study drug related within 15 days of drug administration.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 3% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set.If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

Number of deaths resulting from SAEs suspected to be related to study treatment and number of deaths resulting from SAEs irrespective of causality will be provided.

The adverse events will be summarized for the following subgroup.

- Sex (male vs female)
- Age group (6 - <12, 12 - <18, 18 - <65, >=65 yrs)
- Race

Algorithms for date imputations is provided in Appendix 5.

2.8.1.1 Adverse events of special interest / grouping of AEs

The adverse events of special interest (AESI) are defined in the Case retrieval Sheet (CRS) which is updated for each MedDRA dictionary. The CRS data are stored in RDCRS SAS dataset corresponding to a subset of Ecrs SAS view for which the following filtering criteria are applied

- DRGNAM = “EGA230”

-the latest version of MedDRA at the time of final database lock.

-End date is null (this means this is the latest CRS version). Potential risks based on the current CRS are listed in Table 2-3.

The number and percentage of patients with these special AEs will be summarized. In addition, listings of related adverse events will be provided.

Adverse events of special interest are also analyzed as flagged by the investigator on the eCRF.

Newly occurring liver enzyme abnormalities and QTcF (QT interval corrected for heart rate according to Fredericia) abnormalities will be summarized. QTcF will be summarized in post-text tables and will be presented in the listing. (see Sections 2.8.2 and 2.8.3.1).

Table 2-3 List of safety topics of interest

Safety Topic Of Interest	SOC	MedDRA Code	MedDRA Term	MedDRA Level	MedDRA Qualifier
QTc prolongation	Investigations	20000001	Torsade de pointes/QT prolongation	SMQ	Broad
Increase in liver enzymes and bilirubin	Hepatobiliary disorders	20000006	Drug related hepatic disorders-comprehensive search	SMQ	Broad

2.8.2 Laboratory data

Descriptive statistics will be generated for all clinical laboratory tests performed (actual values and changes from baseline, where applicable) for three groups of laboratory tests (Hematology, Biochemistry, Liver function test and Stool test) by laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values and will be calculated as:

change from baseline = post baseline value – baseline value

The following laboratory parameters will be analyzed for hematology test group: Hematocrit, Hemoglobin, Eosinophil/Leucocytes and Eosinophil count, Erythrocyte sedimentation rate (ESR).

The following laboratory parameters will be analyzed for Liver function test group Alkaline phosphatase, ALT , AST, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, PT/INR, Albumin and GGT.

The following laboratory parameters will be summarized for Biochemistry test group at baseline visit: Sodium, Potassium, Magnesium and Calcium. No change from baseline will be presented as this assessments are done only at baseline visit.

Shift tables using the low/normal/high classification will be used to compare baseline to each post-baseline value of hematology and liver function test parameters.

Furthermore, the number and percentage of patients with newly occurring abnormalities in liver function tests will be summarized by treatment and at any time post-baseline considering all post-baseline data from scheduled, unscheduled and premature discontinuation visit. Abnormalities in liver function tests are defined in Table 2-4.

Table 2-4 Liver-related events

Parameter	Criterion
ALT	>3xULN; >5xULN; >8xULN;>10xULN
AST	>3xULN; >5xULN; >8xULN >10xULN;
ALT or AST	>3xULN; >5xULN; >8xULN >10xULN;
ALT or AST and TBL	ALT or AST > 3 × ULN and TBL > 2 x ULN ALT or AST > 5 × ULN and TBL > 2 x ULN ALT or AST > 10 × ULN and TBL > 2 x ULN
TBL	>1.5xULN, >2xULN
ALP	>2xULN, >3xULN
ALP & TBL	ALP >3xULN & TBL >2xULN
(ALT or AST) & TBL & ALP	ALT or AST >3xULN & TBL >2xULN & ALP <2xULN **(Hy's Law**)

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur at the same day. A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline.

Peak ALT/AST and peak TBL will be plotted using eDISH (evaluation of Drug Induced Serious Hepatotoxicity) method and Modified eDISH (mDISH) method, see Lin, *et. al.* (2012).

For TSR stool test, frequency tables will be presented. Number and percent of patients in each category will be presented by visit. For Egg count using Kato-Katz test summary statistics will be provided by visit.

Laboratory measurements, which are recorded as below the assay detection limits, will be imputed as half of the detection limit; and that above the detection limit will be imputed as upper detection limit, for the summary statistics.

2.8.3 Other safety data

2.8.3.1 ECG and cardiac imaging data

The following quantitative variables will be summarized for averaged triplicate ECG: heart rate, RR interval, PR interval, QRS interval, QT interval and QTcF. Summary statistics for change from baseline will be presented for ECG variables by timepoint and treatment group.

QT intervals will be summarized categorically by computing the number and percentage of patients at each time point and at the maximum post baseline value for the following categories:

- QT, QTcF
  - New ≥450 and < 480 ms
  - New ≥ 480 and < 500 ms
  - New ≥ 500 ms
  - Increase from baseline of ≥ 30 ms to < 60ms
  - Increase from baseline of ≥ 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New > 120 ms

A listing of all newly occurring or worsening abnormalities will be provided.

2.8.3.2 Vital signs

The following quantitative variables will be summarized: Weight (kg), Temperature (^{o}C), Pulse (beats/min), Supine systolic blood pressure (mmHg) and Supine diastolic blood pressure (mmHg).

Analysis in vital sign measurement using descriptive summary statistics for the change from baseline for each post-baseline visit will be performed by vital sign and treatment group.

Change from baseline will only be summarized for patients with both baseline and post-baseline values and will be calculated as:

Change from baseline = post-baseline value – baseline value

The number and percentage of patients with newly occurring notable vital signs will be presented at any time post-baseline. Criteria for notable vital sign abnormalities are provided in Table 2-5 below.

Table 2-5 Criteria for notable vital sign abnormalities

Vital sign (unit)	Patients age at visit		
	6 - 18 years		≥ 18 years
Systolic blood pressure (mmHg)	≥ 95th /≤ 5th percentile of the age and height group[1]		≥ 180 mmHg/≤ 90 mmHg with increase/decrease from baseline of ≥ 20 mmHg
Diastolic blood pressure (mmHg)	≥ 95th /≤ 5th percentile of the age and height group[1]		≥ 105 mmHg/≤ 50 mmHg with increase/decrease from baseline of ≥ 15 mmHg
Pulse (beats/min) [2]	6 – 8 yrs	> 111/< 74 bpm	≥ 120 bpm/≤ 50 bpm with increase/decrease from baseline of ≥ 15 bpm
	8 – 12 yrs	> 103/< 67 bpm	
	12 – 15 yrs	> 96/< 62 bpm	
	≥ 15 yrs	> 92/< 58 bpm	
Temperature (°C)	≥ 38.4/≤ 35.0 °C		>=37.5 (axillary) or >=38.0 (other routes)
Weight	Increase/decrease from baseline[3] of ≥ 2 BMI-for-age percentile categories[4]		Increase/decrease > 7% from baseline

A listing of all newly occurring or worsening abnormalities will be provided.

2.9 Additional analyses to assess the impact of COVID-19 pandemic

Number and percentage of patients with any COVID-19 related screening or study discontinuations will be summarized by discontinuation reason and relationship to COVID-19 pandemic. FAS will be used for summary of study discontinuation.

Number and percentage of patients with COVID-19 related deviations will be summarized by deviation term and relationship to COVID-19 pandemic. FAS will be used for summary.

CCI

2.11 Periodic annual interim reports

Periodic annual interim reports are planned for submission to the US FDA.

Safety laboratory data and adverse events will be monitored continuously throughout the study using data management's data review reports.

Below is the outline of the data required for Periodic annual interim reports.

Table 2-6 Specification of data outputs for Periodic annual interim reports

Output	Analysis set	Periodic annual interim reports
Baseline		
Patient disposition	FAS	Yes
COVID-19 related study discontinuations	FAS	Yes
Protocol deviations	FAS	Yes
Protocol deviations by patient level	FAS	Yes
Analysis population	FAS	Yes
Demographic characteristics	FAS	Yes
Background disease characteristics	FAS	Yes
Safety		
Concomitant medications/significant non-drug therapies	Safety	Yes
Relevant medical history/current medical condition	Safety	Yes
Drug exposure	Safety	Yes
Overview of adverse events	Safety	Yes
All adverse events and Serious adverse events by SOC and PT	Safety	Yes
All adverse events by subgroup age and sex	Safety	Yes
All adverse events by patient level	Safety	Yes
Newly occurring liver enzyme abnormalities (categorical analysis)	Safety	Yes
Hematology/liver parameters summary statistics	Safety	Yes
Hematology shift table	Safety	Yes
eDISH and mDISH plots	Safety	Yes
ECG summary statistics	Safety	Yes
ECG notables	Safety	Yes
Vital signs summary statistics	Safety	Yes
Vital signs notables	Safety	Yes
Abnormal lab/ECG/vital signs listing	Safety	Yes
Efficacy		
Clinical response (Day 10)	FAS	Yes
Clinical Cure (D30, D60, D90)	FAS	Yes
Parasitological cure	FAS	Yes
Response at Day 90 by country	FAS	Yes

3 Sample size calculation

No hypotheses have been specified for the trial and assessment of power is not appropriate. Based on the "rule of three", if a certain serious adverse event or adverse event did not occur within "n" subjects, a 95% CI for the rate of occurrences ranges from 0 to 3/n. It is estimated

that about 300 subjects need to be enrolled for the safety assessment so that the upper bound of the 95% CI is ≤ 1% if a certain event did not occur.

4 Change to protocol specified analyses

NA.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

The study drug administration date should be complete since it's taken in the hospital. In case of missing or partial dates, the visit date will be used as the study drug administration date.

5.1.2 Imputation of parasitological cure

In case of missing stool assessments at post baseline visits, parasitological cure is imputed as cured if stool test assessments at two consecutive prior visits are negative. Else parasitological cure is imputed as not cured.

5.1.3 AE date imputation

The following missing dates will not be imputed

- Missing AE start dates
- AE start dates with missing year
- Partial/missing AE end dates

For other type of missing dates, rules specified in Table 5-1, 5-2 to 5-3 will be used

Table 5-1 AE/Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

Table 5-2 describes the possible combinations and their associated imputations. The upper text indicates the imputation (NC, A, B, C etc.) and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-2 Imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The legend to the above table is shown in Table 5-3.

Table 5-3 Imputation algorithm legends

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

Few examples are shown in Table 5-4.

Table 5-4 Example scenarios

Partial AE start date	Treatment start date	Relationship with TRTSTD	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

5.1.4 Medication/therapy date imputation

5.1.4.1 Prior medications/therapies date imputation

Start date: The same rule which is applied to the imputation of AE start date will be used with the exception that: for scenario (B) the start date will be replaced by the enrollment date/treatment start date -1.

End date:

- Imputed date = min (reference end date, DEC 31 of the year), if month and day are missing.
- Imputed date = min (reference end date, last day of the Month), if day is missing.

where reference end date will be enrollment date/treatment start date.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date. If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.4.2 Concomitant medications/therapies date imputation

Missing concomitant medication/therapy dates will be imputed similar as to AE dates.

5.1.4.3 Post medications/therapies date imputation

Start date:

- If Day is missing, then impute to the max (reference start date, first day of the month).
- Day and month are missing then impute to the max(reference start date, Jan 1)
- Reference start date will be last date of study treatment administration + 1.

End date: No imputation.

5.1.5 Other imputations

NA.

5.1.6 Visit windows

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the Day 10 visit of a patient is delayed and occurs on Day 14, say, it will be re-aligned to visit window Day 15. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a patient may fall in a particular visit window (either scheduled or unscheduled). Statistical approaches to handle multiple assessments in a given visit window are specified below.

- Of note, patients are allowed to have gaps in visits. All data collected will be displayed in listings.
- The following rules are used to determine the window for other visits post baseline:
  - "Lower limit" = "upper limit of prior applicable visit" + 1.
  - "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2 with the exception of Day 90
  - No upper limit for Day 90 visit

For assessments that are scheduled to be performed only once on a day, Table 5-5 describes the analysis windows mapping to visits (not just scheduled visits) based on study days alone. Repeat and/or unscheduled visits (which will be numbered in the database according to new NCDS standards) will be mapped for analysis purposes in the same way. If there are multiple measurements within an analysis window, the conventions defined in Table 5-6 will be used to determine the appropriate measurement to be selected for analysis.

The mapped visits will be used in the by visit analyses. However, the listings will show the collected data regardless of used in the by visit analyses.

Table 5-5 Analysis visit windows based on study days alone

Analysis Visit	Target Day	Analysis window for assessment group			
		Clinical Signs and Symptoms	Stool Sample Test/Ultrasound/ Hematology/ Liver function test	Vital signs and body temperature	ECG
Baseline	1	Up to Day 1	up to day 1	Up to Day 1	Up to Day 1
Day 1 to 2	1-2(4-5 hrs after 1st dose)	NA	NA	NA	1-2(4-5 hrs after 1st dose)
	1-2(4-12 hrs after 2nd dose)	NA	NA	NA	1-2(4-12 hrs after 2nd dose)
Day 3	3	Day 2 – 4	NA	Day 2 – 4	NA
Day 6	6	Day 5 – 7	NA	Day 5 – 7	NA
Day 10	10	Day 8 – 12	Day 2 – 20	Day 8 – 20	NA
Day 15	15	Day 13 – 22	NA	NA	NA
Day 30	30	Day 23 – 37	Day 21 – 45	Day 21 – 45	NA
Day 45	45	Day 38 – 52	NA	NA	NA
Day 60	60	Day 53 – 67	Day 46 – 75	Day 46 – 75	NA
Day 75	75	Day 68 – 82	NA	NA	NA
Day 90/End of study	90	Day 83 and above	Day 76 and above	Day 76 and above	NA

Table 5-6 Rules for flagging variables

Timing of measurement	Type of data	Rule
Baseline	All data	The last measurement made prior to and including administration of the first dose of study treatment – note this may include measurements taken on the day of enrollment. If a patient did not receive any dose of study treatment then the enrollment date will be used.
Post-baseline efficacy	All data	The measurement closest to the target day/time will be used. In the event that two measurements are taken equally apart (e.g. 1 day before target date and 1 day after) the first one will be used.
Post-baseline safety	Summary visit information (e.g. lab, ECG, etc.)	The measurement closest to the target day/time will be used. In the event that two measurements are taken equally apart, the first one will be used.
Post-baseline safety	Notable abnormalities (e.g. lab, ECG, VS)	The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window

5.2 Prohibited Medication

Following medication class will be considered as prohibited;

1) Anthelminitcs throughtout the entire study, except as rescue medication.
2) Medications with known risk of Torsades de Pointes within 4 days after the last dose
3) Any medication which is a CYP2C19 substrate requiring therapeutic drug monitoring (such as (S)-mephenytoin) within 4 days after the last dose.

However individual concomitant medications will be reviewed and those falling in the category of prohibited medication class will be flagged as prohibited medication during clinical data review.

5.3 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

5.4 Laboratory parameters derivations

Grade categorization of liver function tests will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version 4.0 at the time of analysis will be used.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used.

5.5 Statistical models

5.5.1 Primary analysis

The primary analysis is detailed in Section 2.5.

5.5.2 Key secondary analysis

NA.



5.6 Rule of exclusion criteria of analysis sets

Table 5-7 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
FAS	NA	Mistakenly enrolled into the study.
SAF	NA	No study drug taken

6 Reference

1. Blood pressure percentiles are calculated for each blood BP record using the method described in Appendix B of the following reference: The Fourth Report on Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents. Pediatrics 2004; 114; 555
2. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI:10.1016/S0140-6736(10)62226-X.
3. Baseline BMI-for-age weight status categories are underweight (less than the 5th percentile), healthy weight (5th percentile to less than the 85th percentile), overweight (85th to less than the 95th percentile) and obese (equal to or greater than the 95th percentile)
4. BMI-for-age percentiles categories (P3, P5, P10, P25, P50, P75, P85, P90, P95, P97) are obtained from the WHO Growth Charts (https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age)