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EGA230

Clinical Trial Protocol CEGA230B2404 / NCT04230148

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

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulation
CI	Confidence Interval
CRF	Case Report Form (paper or electronic)
CRO	Contract Research Organization
CT	Computed Tomography
CTT	Clinical Trial Team
CMO & PS	Chief Medical Office and Patient Safety
CRA	Clinical Research Associate
DLT	Dose Limiting Toxicity
DDE	Direct Data Entry
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
eSAE	Electronic Serious Adverse Event (eSAE form)
ESR	Erythrocyte sedimentation rate
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
LFT	Liver function test
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)
PD	Pharmacodynamics
PK	Pharmacokinetics
PMC	Post Marketing Commitment

PT	Prothrombin time
QMS	Quality Management System
QTcF	QT Interval Corrected by the Fridericia Correction Formula
SAE	serious adverse event
SAF	Safety Set
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TdP	Torsades de pointes
TSR	Rapid Sedimentation Technique
ULN	Upper Limit of Normal
USA	United States of America
USPI	United States Prescribing Information
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Off-site healthcare Professional	A qualified healthcare professional, e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Patient	An individual with the medical condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, (example a home or another appropriate location)
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment 1 (15-Mar-2021)

Amendment Rationale

The primary purpose of this amendment is to incorporate safety ECG monitoring for a subset of patients enrolling into the study who may be at increased risk of QT prolongation. This follows the recent results of a Thorough QT (TQT) study (CEGA230B2102) which confirmed pre-clinical findings seen with Egaten.

In the CEGA230B2102 study, healthy subjects dosed at the same therapeutic dose planned for the CEGAB230B2404 study (10 mg/kg BID for 1 day) showed a peak mean placebo-corrected ΔQTcF of 9.2 msec, whilst those dosed at the supratherapeutic dose (10 mg/kg BID for three days) showed peak mean placebo-corrected ΔQTcF of 21.7 msec. There were no treatment-related adverse events and no severe or serious adverse events reported in the study. Furthermore, no QTc related safety issues have been reported despite exposure to almost 2 million Patient Treatment Courses (PTC) of Egaten [Edition 1 Egaten Investigator Brochure] in the post-marketing setting. In line with the primary objective of the study, ECG monitoring will be conducted amongst those patients who, at screening, have QTcF ≥ 450 msec- <480 msec or are taking medications which are CYP1A2 modulators. Since the highest mean QTcF was observed at 4 hours in the TQT study, ECG will again be assessed 4 hours after first dose of Egaten and at 4-12 hours after the second dose for these patients. Patients with a resting QTcF ≥ 480 msec at screening will not be included in the study.

Other changes include:

- Change to the minimum weight requirement for study entry to exclude underweight pediatric patients and the possibility of overdosing.
- Addition of a pre-screening period, for logistical reasons, to allow sites the option to conduct study-required ELISA diagnostic testing beyond the relatively short Screening window.
- Distinction between the evaluation of patients at Day 10, and at later time points, since patients are not expected to reach clinical cure at the earlier time.
- Addition of cardiac safety monitoring for monitoring and management of adverse events related to cardiac arrhythmia.
- Updated safety monitoring period following subject discontinuation from study drug, given that end of study visit is beyond 30 days after end of treatment.
- Updates regarding measures that may be taken by the sites in the event of Public Health Emergencies.

Other minor changes/ corrections in the protocol text, tables and footnotes were made for the consistency and/or clarifications

Study Status

The CEGA230B2404 study has not begun enrollment yet.

Changes to the Protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. The following changes have been made：

- Section 2, 8.3, 12.5, Table 2-1: Updated to distinguish between Day 10 efficacy evaluations, and at later time points.
- Section 3, 4.5, 5.2, 6.2.2, 6.5.3, 6.5.4, Table 8-1, Table 8-6, Section 8.4.2, 9.1.1, 10.2.2: Updated as a result of additional ECG monitoring in the study.
- Section 3,4.6, 6.7, 7, 8 : Updated for cases of Public Health Emergency and inclusion of remote procedures.
- Section 3, figure 3-1 to include optional pre-screening.
- Section 5.1: Updated for exclusion of underweight pediatric patients.
- Section 5.2: Exclusion criteria added for clinically relevant abnormalities of electrolyte balance which require correction.
- Section 6.1.3, Table 6-2: Updated for dosing clarification to align with the FDA label.
- Section 6.3.1, Table 8-1, Section 10.1.1: Updated to allow pre-screening to be conducted in the study.
- Table 8-1: Included Biochemistry, body measurements updated as height and weight, updated information in legend for ELISA, Stool examination and assessments done as part of standard of care within screening period.
- Section 8.1.1: Updated information for re-screening.
- Section 8.3: Treatment failure definition updated.
- Section 8.4, Table 8-5: Included Biochemistry evaluations.
- Section 9.1.1, 9.1.2, 9.1.4 : Protocol text updated.
- Section 9.2, 10.1.1, 10.1.3: Updated for clarification of period for AE/SAE reporting.
- Section 10.2.2 for cardiac safety monitoring.
- Section 13.5 newly included to cover participant engagement.

Other minor changes/ corrections in the protocol text, tables and footnotes were made for the consistency and/or clarifications.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC and relevant Health Authority approval prior to implementation.

The changes herein affect the Informed Consent/Assent. Sites are required to submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CEGA230B2404
Full Title	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.
Brief title	Study of safety, tolerability and efficacy of Egaten in fascioliasis patients (6 years of age or older).
Sponsor and Clinical Phase	Novartis/Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The study is a Post Marketing Commitment (PMC) to the Food and Drug Administration (FDA) and will evaluate safety and tolerability along with clinical outcomes of Egaten 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). The study is being conducted in alignment with FDA recommendation, post approval as an open label, single-arm study. There is no placebo arm in the study as treating such subjects with placebo is unethical.
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.
Secondary Objectives	To evaluate clinical response in acute and chronic fascioliasis subjects at Day 10. To evaluate clinical cure rate in acute fascioliasis subjects at Day 30, Day 60 and Day 90. To evaluate clinical cure rate of chronic fascioliasis subjects at Day 30, Day 60 and Day 90. To evaluate parasitological cure rate of chronic fascioliasis subjects at Day 10, Day 30, Day 60 and Day 90.
Study design	This is a multicenter, open label, non-comparative, single arm multi-country 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, but 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.

Population	The study population consists of male and female adult and pediatric patients (≥ 6 years of age). The study will enroll approximately 300 subjects with acute (minimum 15% of overall study population) or chronic fascioliasis.
Key Inclusion criteria	1. Written informed consent must be obtained before any study protocol specific assessment is performed other than procedures performed as part of standard of care. a. Parental/legal guardian informed consent must be obtained and signed for pediatric subjects (formally documented and witnessed, via an independent trusted witness) prior to any study related procedure. b. Subjects < 18 years old, who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines. c. If the subject is unable to read and write or otherwise incapable of signing an informed consent, then a witnessed consent according to local ethical standards is permitted. 2. Subjects (Adult and pediatric subjects ≥ 6 years of age and ≥ 18 kg of weight) with confirmed diagnosis of fascioliasis.
Key Exclusion criteria	1. Subjects diagnosed with ectopic fascioliasis, extrahepatic involvement (e.g., lungs, spleen, pancreas, subcutaneous tissue, gastrointestinal organs, etc.). 2. Subjects with known hypersensitivity to triclabendazole /other benzimidazole derivatives and/or any of the excipients in Egaten 3. Subjects taking any anthelmintic medications within two weeks or 5 half-lives, whichever is longer prior to enrolling into study. 4. Inability or unwillingness to undergo study related procedures. 5. Subjects who in the judgment of the Clinical Investigator are unsuitable for the trial or who have to be excluded in order to be compliant with local fascioliasis management guidelines that may differ from the FDA approved label, including but not limited to : • Subjects who are machine operators or drivers. • Medical history of liver (other than fascioliasis), kidney or cardiac disease. 6. Females (including under the age of 18) known to be pregnant or testing positive for pregnancy at screening. 7. Lactating women unwilling to discontinue lactation up to 72 hours after the second dose administration or as per local guidelines. 8. Subjects requiring therapeutic drug monitoring of CYP2C19 substrate(s) (e.g. S-mephenytoin). 9. Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia. 10. Subjects with medical history of QT prolongation or a history of symptoms compatible with a long QT interval or on medication which prolong the QT interval. 11. Patients with a resting QTcF ≥480 msec or inability to determine the QTcF interval at screening.
Study treatment	Novartis will supply the study treatment drug, Egaten (Triclabendazole) 250 mg tablets, which will be given to the study subjects in an open label manner. When possible both doses will be administered under supervision and if not, at least the first dose will be administered under the supervision of site personnel.

Key efficacy assessments	Efficacy assessments will consist of clinical signs and symptoms, lab tests, ultrasound and stool examination and will be performed on Day 10, Day 30, Day 60 and Day 90. • Acute and chronic fascioliasis: clinical response on Day 10, evaluating improvement or resolution of baseline clinical signs and symptoms • Acute Fascioliasis: Clinical cure on Day 30, Day 60 and Day 90, which takes into consideration resolution of baseline clinical signs and symptoms, improvement in baseline lab parameters and improvement in baseline ultrasound findings of Fascioliasis. • Chronic fascioliasis: Parasitologic cure, defined as absence of Fasciola eggs in feces on Study Day 10, Day 30, Day 60 and Day 90 confirmed by stool examination. • Chronic fascioliasis: Clinical cure on Day 30, Day 60 and Day 90, which takes into consideration resolution of baseline clinical signs and symptoms, improvement in baseline lab parameters and improvement in baseline ultrasound findings of Fascioliasis.
Key safety assessments	Evaluation of all Adverse events (AEs) and Serious Adverse events (SAEs), ECG monitoring, physical examination, vital signs, and laboratory assessments (Hematology, Biochemistry, Liver function test, Stool test) will be conducted as part of safety assessments.
Data analysis	The primary analyses will be based on summary statistics. For secondary analyses, the proportion and confidence interval of subjects who are clinically cured and/or parasitological cured will be calculated.
Key words	Post-Marketing commitment study, Fascioliasis (acute or chronic), triclabendazole, parasitological cure.

1 Introduction

1.1 Background

Fascioliasis is caused by the trematode flukes *Fasciola hepatica* and *Fasciola gigantica*; the former has a worldwide distribution, and the latter is primarily found in tropical regions, although the two species overlap in some regions, mainly in Asia and the Middle East (Mas-Coma et al 2009).

Fasciola flukes mainly infest goats, cattle and sheep, but also cause disease in humans following ingestion of contaminated food or water (Nyindo and Lukambagire 2015). Liver fluke development is dependent on environmental factors as infection of definitive (livestock) and intermediary (snails) hosts requires freshwater. Various environmental factors have created hypo- and hyper-endemic area of the infection across different continents with some regions showing predominantly one species infection (F. hepatica or F. gigantica) vs. others showing overlap of both species infection (Mas-Coma 2005).

Subjects with fascioliasis may present either in acute stage (sometimes referred to as hepatic or invasive) or in chronic stage (sometimes referred to as biliary) (Mas-Coma et al 2014). Acute disease, which may last for 3-5 months, is considered to be associated with migration of flukes into the bile ducts, and may be accompanied by fever, intense abdominal pain, gastrointestinal disturbances (loss of appetite, flatulence, nausea, diarrhea), urticaria, ascites, painful hepatomegaly, splenomegaly, anemia, jaundice and eosinophilia, the latter potentially reaching very high levels. Rarely, respiratory symptoms may also occur (Arjona et al 1995, Millán et al 2000, Marcos et al 2008, Kaya et al 2011). In chronic disease, when adult flukes are residing in the bile ducts, the resulting inflammation and hyperplasia of the epithelium, together with the physical presence of the parasite, may lead to biliary obstruction. Biliary colic, epigastric pain, jaundice, and right upper-quadrant abdominal tenderness may occur during this phase of infection. Hepatic enlargement may occur, associated with splenomegaly or ascites (Arjona et al 1995, Keiser et al 2005, Marcos et al 2008, Goral et al 2011). Gallstones, in the bile duct or gall bladder are common (Millán et al 2000, Hawramy et al 2012). Chronic disease may be very long-lasting, with up to a duration in excess of 10 years (Marcos et al 2008). The diagnosis of fascioliasis can be challenging, as many features of the disease (such as gastrointestinal symptoms and eosinophilia) are non-specific (Cabada and White 2012).

Diagnosis of the acute fascioliasis is usually clinical on the basis of a combination of clinical symptoms and signs, laboratory evaluations (notably eosinophilia), imaging (most commonly ultrasonography or computed tomography (CT) scanning). It is confirmed using serological testing with enzyme-linked immunosorbent assay (ELISA test). Diagnosis of chronic fascioliasis is parasitologic, with the diagnosis predominantly based on coprologic antigen tests, and detection of Fasciola eggs in feces or duodenal aspirates. Detection of Fasciola eggs, while providing a definitive diagnosis is considered to be possible only in chronic disease (where adult flukes are present in the biliary tract); acute fascioliasis remains more difficult to identify, although serology is useful and imaging may be more sensitive and specific than in chronic disease (Marcos et al 2008, Fica et al 2012, Nyindo and Lukambagire 2015).

Many anthelmintic agents and artemesinin derivatives have been investigated for treating human fascioliasis (Keiser and Morson 2008). The treatment of choice is triclabendazole (Egaten, 6-chloro-5-(2,3-dichlorophenoxy)-2-(methylthio)-1H-benzimidazole), which is a

narrow-spectrum anthelmintic agent (Pan American Health 2010, Centers for Disease Control 2017). It was originally developed to treat fascioliasis in domestic livestock (Pan American Health 2010, Kelley et al 2016,). In animals, a single dose is effective against Fasciola flukes, although the exact mechanism of action is unclear (Kelley et al 2016). It is the only treatment for fascioliasis recommended by the World Health Organization (WHO) and the Pan American Health Organization (Pan American Health 2010) and is the drug of choice as per the US Centers for Disease Control and Prevention (Centers for Disease Control 2017). The drug is made available to patients in several endemic countries by the WHO, including in Bolivia, Georgia, Madagascar, Peru, Vietnam and Yemen.

EGATEN™ (triclabendazole) was approved by the national regulatory agencies in France (2002) and Egypt (1997) with the recommended single dose of 10 mg/kg based on the subjects body weight for the treatment of fascioliasis in subjects 6 years of age and older. Recently it was approved in US (February 2019) at a dosing regimen of two 10 mg/kg doses given 12 hours apart.

This study is planned to be conducted as per PMC to US FDA; it will be an open-label, single-arm study to assess outcomes of treatment with two 10 mg/Kg oral doses of Egaten given 12 hours apart in patients with fascioliasis.

1.2 Purpose

The study will evaluate safety and tolerability along with clinical outcomes of Egaten administered as per the FDA approved dosing regimen of 2 doses of 10 mg/kg (given approximately 12 hours apart) in approximately 300 Fascioliasis subjects (≥ 6 years of age).

2 Objectives and endpoints

The study will assess overall safety, tolerability and clinical outcomes of Egaten administered as two 10 mg/kg doses given approximately 12 hours apart in subjects with fascioliasis.

Table 2-1 Objectives and related 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.

3 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, but subjects with acute/symptomatic disease or requiring post-dose ECG monitoring could be hospitalized at investigator's discretion.

Screening of patients for inclusion in the study may happen in two stages: Pre-screening and Screening. Pre-screening is optional to allow sites to successfully identify subjects with fascioliasis prior to screening visit. Subjects completing the pre-screening part will also undergo screening procedures for eligibility to participate in the study and the ELISA assessment need not be repeated at screening visit, if it was conducted within the pre-screening window. Further information is provided in Section 8.

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.

Additional unscheduled follow-up visits in person and/or by phone may be performed as per investigator's medical judgement.

Remote Procedures

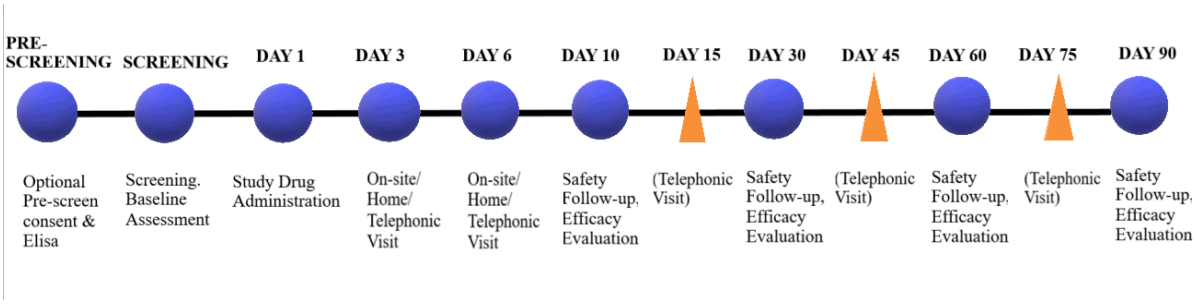
At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures (see Table 8-1 Assessment schedule) performed at a remote location.

Procedures performed remotely will still be under the oversight of the Investigator, who retains accountability for the oversight and all efficacy and safety decisions, with delegation of tasks to an off-site healthcare professional.

If allowed by the country regulations and depending on operational capabilities, the Home nursing service may be implemented according to country requirements to ensure continuity of patient treatment as per the Principal Investigator (PI) discretion.

For example, home nursing visits may be applicable in situations such as health conditions, quarantines, site closures, and travel limitations, where participants may not be able to travel to the investigational site for protocol-specified visits. These remote procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This study is a PMC to the US FDA to assess the safety, tolerability and clinical outcomes of the US FDA approved dosing regimen of Egaten (two doses of 10 mg/kg given 12 hours apart). As part of this commitment to FDA, Novartis aims to collect safety, tolerability and efficacy data in approximately 300 subjects with fascioliasis. The study is being conducted in alignment with FDA recommendation, post approval as an open label, single-arm study with two doses of 10 mg/kg of Egaten given approximately 12 hours apart in subjects with fascioliasis. There is no placebo arm in the study as treating such subjects with placebo is unethical.

4.2 Rationale for dose/regimen and duration of treatment

Since the study is a post-marketing commitment study for FDA, the study dosing regimen is as approved by the US FDA and is part of approved label for Egaten in the US (Hien et al 2008). The US FDA approved dose regimen is based on the data from various past studies, case reports and case series by third parties, the CIBA company sponsored/WHO sponsored studies, the Egyptian government studies, and recommended for the sponsor's named patient program, dosages used in veterinary medicine, pharmacokinetics (PK) in humans, and early published

case reports of successful treatment of human fascioliasis (Wessely et al 1988, Loutan et al 1989, WHO 2019).

Early in the development of triclabendazole for human use, dose regimens were explored in two of the WHO studies (Study CEGA230B2208 in pediatric subjects in Bolivia, and Study CEGA230B2201 in Iran), and in two of the studies performed by the Egyptian government (Studies CEGA230B2209 and CEGA230B2211). In these studies, doses of 10 mg/kg were found to be effective and well -tolerated. Some more recent third party studies, including the randomized study by (Maco et al 2015) and the study by (Talaie et al 2004), assessed different dosing regimens. Single doses of 10 mg/kg (repeated if necessary) were generally found to be effective and well tolerated. Egaten should be dosed with food on the basis of the data from the pharmacokinetic studies. The two pharmacokinetic studies (CEGA230B2215 and CEGA230B2214) suggest that there is greater exposure to triclabendazole and its active metabolite when dosed under fed condition.

The initial dosing recommendation of Egaten 10 mg/kg was based on earlier studies (CEGA230B2209 and CEGA230B2211). However, more recent third party studies found twice repeated dose of Egaten 10 mg/kg in a day to be effective (Talaie et al 2004, Maco et al 2015). In addition, the dosing regimen of two doses of 10 mg/kg given approximately 12 hours apart is consistent with the Fascioliasis treatment guidelines from the WHO and most endemic countries (WHO 2019). The WHO recommended regimen is 10 mg/kg body weight administered as a single dose in both clinical practice and preventive chemotherapy interventions. In clinical practice, where treatment failure occurs, the dosage may be increased to 20 mg/kg body weight in two divided doses 12-24 hours apart (WHO 2019).

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Not applicable.

4.4 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned for the study.

4.5 Risks and benefits

Triclabendazole has been demonstrated to be effective in acute and chronic fascioliasis, in both adult and pediatric subjects in clinical trials in endemic areas and in use in epidemic situations. The evidence supporting human use of triclabendazole is derived from a variety of sources, including data generated by the Sponsor, the WHO, and by third party investigators. As no suitable active comparators are available when most of the studies were performed, and the use of placebo controls would be both ethically difficult and of dubious value (as there appears to be very little placebo effect in the treatment of fascioliasis), the study is planned as an open label study. Overall, the available evidence base clearly and consistently demonstrates that triclabendazole is highly effective in the treatment of fascioliasis and that is a potential benefit for the subjects participating in the study. Triclabendazole is well tolerated in the treatment of fascioliasis. The main adverse events (AE) observed (abdominal, epigastric, and hypochondrial pain, characterized as biliary colic, potentially associated with obstructive jaundice and elevations in serum levels of hepatic enzymes) are related to expulsion of dead or dying flukes

from the biliary tract. A thorough QT study (CEGA230B2102) showed triclabendazole caused prolongation of QTc interval with a mean peak of placebo-corrected increase from baseline of 9.2 msec with the therapeutic dose (2 doses of 10 mg/kg given 12 hours apart). Due to QT prolongation, there is a potential risk for Torsades de Pointes (TdP) with triclabendazole in patients with other risk factors for QT prolongation. Apart from this, risks to subjects appear to be minimal, particularly given the very short treatment duration (in most cases a single dose) and fairly rapid elimination of triclabendazole and its metabolites. Other common AEs following triclabendazole administration included headache, dizziness and vertigo.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

The study population consists of male and female adult and pediatric patients (≥ 6 years of age). The study will enroll approximately 300 subjects with acute (minimum 15% of overall study population) or chronic fascioliasis.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any study protocol specific assessment is performed other than procedures performed as part of standard of care.
   a. Parental/legal guardian informed consent obtained and signed for pediatric subjects (formally documented and witnessed, via an independent trusted witness) prior to any study related procedure.
   b. Subjects < 18 years old, who are capable of providing assent, must provide assent with parental/legal guardian consent or as per local ethical guidelines.
   c. If the subject is unable to read and write or otherwise incapable of signing an informed consent, then a witnessed consent according to local ethical standards is permitted
2. Subjects (Adult and pediatric subjects ≥ 6 years of age and ≥ 18 kg of weight) with confirmed diagnosis of fascioliasis.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Subjects diagnosed with ectopic fascioliasis, extrahepatic involvement (e.g. lungs, spleen, pancreas, subcutaneous tissue, gastrointestinal organs, etc.).
2. Subjects with known hypersensitivity to triclabendazole and/or to other benzimidazole derivatives or to any of the excipients in Egaten.

3. Subjects taking any anthelmintic medications within two weeks or 5 half-lives, whichever is longer prior to enrolling into study.
4. Inability or unwillingness to undergo study related procedures
5. Subjects who in the judgment of the Clinical Investigator are unsuitable for the trial or who have to be excluded in order to be compliant with local fascioliasis management guidelines that may differ from the FDA approved label, including but not limited to :
   - Subjects who are machine operators or drivers.
   - Medical history of liver (other than fascioliasis), kidney or cardiac disease.
6. Females (including under the age of 18) known to be pregnant or testing positive for pregnancy at screening.
7. Lactating women unwilling to discontinue lactation up to 72 hours after the second dose administration or as per local guidelines.
8. Subjects requiring therapeutic drug monitoring of CYP2C19 substrate(s) (e.g. (S)-mephenytoin).
9. Clinically relevant abnormalities of electrolyte balance which require correction, e.g., hypokalemia, hypocalcemia or hypomagnesemia.
10. Subjects with medical history of QT prolongation or a history of symptoms compatible with a long QT interval or on medication which prolong the QT interval.
11. Patients with a resting QTcF ≥480 msec or inability to determine the QTcF interval at screening.

6 Treatment

6.1 Study treatment

Novartis will supply the study treatment drug, Egaten (Triclabendazole) 250 mg tablets, which will be given to the study subjects in an open label manner. Both doses will be administered under supervision if possible, otherwise, at least the first dose will be administered under the supervision of site personnel.

6.1.1 Investigational and control drugs

Study medication will be made available by the sponsor as the commercial form for "USA" of Egaten 250 mg scored tablets for oral use. The subjects should be instructed to take the tablets orally with food.

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
EGA230(Egaten) 250 mg	Tablet	Oral use	Open label	Sponsor (global)

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Treatment arms/group

In this open label, single arm study, Egaten will be administered to all subjects as two 10 mg/kg doses given approximately 12 hours apart according to the FDA label guidance. The 250 mg tablets are functionally scored and divisible into two equal halves of 125mg. If the dosage cannot be adjusted exactly, round the dose upwards.

6.1.4 Treatment duration

Subjects will be treated with two doses of 10 mg/kg of Egaten given approximately 12 hours apart, with the first dose given on Day 1 under the site supervision. The second dose can be home administration. Subjects will be observed for any vomiting within 1 hour of dosing and instructed to report if they experience vomiting after taking the second dose (if instructed to be taken at home). Re-dosing can be considered once, if the subject vomited within 1 hour of taking either dose.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject is enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication (if required). If in doubt, the investigator should contact the Novartis medical monitor before enrolling a subject. If the subject is already enrolled, investigator can contact Novartis to determine if the subject should continue participation in the study when in doubt.

6.2.2 Prohibited medication

Use of the treatments with other anthelmintics is not allowed after the subject enrolls into the study until the End of Study, except as a rescue medication. Medications which are intended to treat AEs or any other concurrent or comorbid conditions are allowed as per discretion of investigator. Medications with a known risk of TdP should be avoided until 4 days after the last dose (Investigators may refer to www.crediblemeds.org for identifying drugs with known risk of TdP). Any medication which is a CYP2C19 substrate and requiring therapeutic drug monitoring (such as (S)-mephenytoin) should be avoided until 4 days after the last dose.

6.2.3 Rescue medication

Subjects considered non-responders/treatment failures (Section 8.3) based on investigator's assessment may be administered Standard of Care (SoC) treatment as rescue medication as per local Fascioliasis treatment guidelines and/or practice.

Subjects who receive rescue medication will also be followed up for safety till end of the study.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a subject Number (subject No.), that is assigned when the subject is first enrolled for Pre-screening/screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (As assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

No randomization will be performed in this study. For this open label study, study drug will be supplied by Novartis or designated Clinical Research Organization (CRO) to Investigational Sites.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the Clinical trial team (CTT).

6.5 Dose escalation and dose modification

Not applicable.

6.5.1 Dose escalation guidelines

Not applicable.

6.5.2 Definitions of dose limiting toxicities (DLTs)

Not applicable for the study.

6.5.3 Dose modifications

In subjects requiring additional ECG monitoring, if QTcF $\geq$ 500 msec at 4-5 hours after the first dose, discontinue the study treatment.

6.5.4 Follow-up for toxicities

Subjects who present with clinically significant symptoms or detected with abnormal laboratory value(s) should be referred to appropriate clinical experts.

Subjects with fascioliasis are prone to developing liver enzyme elevation and jaundice attributed to the Fasciola worm causing biliary obstruction and biliary colic. Previous studies have shown that some subjects might experience transient increase in the liver enzymes Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) with triclabendazole treatment. The liver enzyme levels in these subjects returned to normal within 1-2 months of treatment. These liver enzyme increases are attributed to irritation of the parasite by triclabendazole treatment with subsequent disintegration and excretion of the dead parasite via the bile duct into the gastrointestinal tract (el-Morshedy et al 1999, Talaie et al 2004). During the study, liver enzymes will be evaluated at baseline, Day 10, Day 30, Day 60 and Day 90; subjects with elevated Liver Function Tests (LFTs) will be followed up by investigators until these return to baseline (Section 16.1). Investigators can consider the guidelines for monitoring of drug-induced liver injury for guidance for follow-up of subjects meeting the criteria of liver injury (FDA 2009).

Triclabendazole was found to prolong QTc interval with a mean peak of placebo-corrected increase from baseline of 9.2 msec with the therapeutic dose (2 doses of 10 mg/kg given 12 hours apart) in a thorough QT study (CEGA230B2102) with healthy volunteers. Therefore, there is a potential risk for Torsades de Pointes (TdP) with triclabendazole in patients with other risk factors for QT prolongation. Approximately 1.8 million patient treatment courses (PTC) of triclabendazole have been used in the post-marketing period till 2017. However, there have been no reports of QTc prolongation in patients treated with Egaten either in clinical studies or with the post-marketing exposure. During the study patients with QTcF $\geq$ 450 msec to <480 msec at screening will be monitored with additional ECG assessments as mentioned in Section 8.4.2. All patients will also be followed up for adverse events including events possibly relating to cardiac arrhythmias as per the follow up visits specified in Table 8-1.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

In the instance that the second dose is given to the subject to be taken at home, the investigator must promote compliance by instructing the subjects to take the study treatment exactly as prescribed and by stressing that compliance is necessary for the subject's successful treatment and for validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance should be monitored throughout the study. This information will be captured in the source document. All study treatment dispensed and returned must be recorded in the Drug Accountability Log or applicable CRF.

6.6.2 Recommended treatment of adverse events

Medication, non-drug therapy etc. for treating adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

As the study is an open label study, emergency breaking of assigned treatment code is not applicable for this study.

6.7 Preparation and dispensation

Each study site will be supplied with packaged study drug as described under investigational and control drugs (Section 6.1.1).

A unique medication number is printed on the study medication label. Investigator will determine the dose required to be dispensed to the subject based on their body weight and Investigator staff will dispense the kit to the subject.

The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the package to the subject, site personnel will detach the outer part of the label from the package and affix it to the subject's source document.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of Investigational medicinal product (IMP) directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. In this case, regular phone calls or virtual contacts will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment and discussion of the participant´s health status until the participants can resume visits at the study site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis country organization quality assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis or designated CRO monitor or to the Novartis or designated CRO address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

There is no additional treatment planned for the treatment of fascioliasis.

6.7.2 Instruction for prescribing and taking study treatment

Advise subjects that Egaten should be taken orally with food. The scored tablets can be swallowed whole or, divided in half and taken with water, or crushed and administered with apple sauce (or alternate). The crushed tablet mixed with apple sauce is stable for up to 4 hours.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation); Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol) other than procedures performed as part of standard of care. The process of obtaining informed consent must be documented in the subject source documents.

Novartis or designated CRO will provide to investigators in a separate document a proposed informed consent form that complies with the ICH, Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

The following informed consents are included in this study:

- Pre-screening consent, which is optional for use by the site.
- Main study consent, which also includes:

  A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study.
- Parent Legal Guardian Consent (for children 6-17 years age)

  A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study.
- Child Assent (7-11 years age)
- Adolescent Assent (12-17 years age)
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

Information about common side effects already known about the investigational drug can be found in United States Prescribing Information (USPI) for Egaten. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug

that is identified between prescribing information updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and advice that in order to participate in the study they must adhere to the appropriate contraception methods.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Heath Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects to be seen for all visits/assessments, except for the telephonic visits, as outlined in the assessment schedule (Table 8-1) or within the protocol allowable time window. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (End of the Study visit) will be performed. At this End of Study visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	**Screening****		**Treatment**	**Follow up**									**Unscheduled**
Visit Name	**Pre-screening**	**Screening/Baseline**	**Treatment**	**FUP 1#**	**FUP 2#**	**FUP 3**	**FUP 4[1]**	**FUP 5**	**FUP 6[1]**	**FUP 7**	**FUP 8[1]**	**End of Study[2]**	**Unscheduled[3]**
Days	**-14**	**-2 to 1**	**1 to 2**	**3 ±1**	**6 ±1**	**10 ±1**	**15 ±2**	**30 ±3**	**45 ±5**	**60 ±5**	**75 ±5**	**90 ±5**	**2 to 90**
Demography		X											
Pre-screen Consent[4]	X												
Informed consent		X											
Inclusion / Exclusion criteria		X											
Medical history/current medical conditions		X											
Physical Examination		S		S[5]	S[5]	S		S		S		S	S
Clinical Signs and Symptoms[6]		X		X	X	X	X	X	X	X	X	X	X
Vital signs, Height and weight		X		X[5]	X[5]	X		X		X		X	X
ECG[7]		X	X										X[10]
Stool Sample Test [8]		X				X[9]		X[9]		X[9]		X[9]	X[10]

Period	**Screening****		**Treatment**	**Follow up**									**Unscheduled**
Visit Name	**Pre-screening**	**Screening/Baseline**	**Treatment**	**FUP 1[#]**	**FUP 2[#]**	**FUP 3**	**FUP 4[1]**	**FUP 5**	**FUP 6[1]**	**FUP 7**	**FUP 8[1]**	**End of Study[2]**	**Unscheduled[3]**
Days	**-14**	**-2 to 1**	**1 to 2**	**3 ±1**	**6 ±1**	**10 ±1**	**15 ±2**	**30 ±3**	**45 ±5**	**60 ±5**	**75 ±5**	**90 ±5**	**2 to 90**
Dose administration[11]			X										
Safety Follow up Call				S	S		S		S		S		
Hospitalization (As required)		X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X
ELISA[12]	X[4]	X											
Ultrasound		X				X		X		X		X	X[10]
Liver function test[13]		X[14]				X[14]		X[14]		X[14]		X[14]	X[10,14]
Hematology[15]		X[14]				X[14]		X[14]		X[14]		X[14]	X[10,14]
Biochemistry[16]		X[14]											X[10,14]
Urine Pregnancy Test[17]		S										S	
Study completion information												X	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor.
[S] Assessment to be recorded in the source documentation only.
Telephonic Visit or Home Visit or Onsite visit depending on the Investigator discretion.

Period	**Screening****		**Treatment**	**Follow up**									**Unscheduled**
Visit Name	**Pre-screening**	**Screening/Baseline**	**Treatment**	**FUP 1#**	**FUP 2#**	**FUP 3**	**FUP 4[1]**	**FUP 5**	**FUP 6[1]**	**FUP 7**	**FUP 8[1]**	**End of Study[2]**	**Unscheduled[3]**
Days	**-14**	**-2 to 1**	**1 to 2**	**3 ±1**	**6 ±1**	**10 ±1**	**15 ±2**	**30 ±3**	**45 ±5**	**60 ±5**	**75 ±5**	**90 ±5**	**2 to 90**

** ELISA assessment if done during the pre-screening period need not be repeated at screening visit. Assessments done or Samples collected as part of standard of care within the screening period and before signing ICF need not be repeated at screening visit

[1] Telephonic visit

[2] End of Study assessments will be performed for all subjects including those who are discontinued during the study prior to Day 90, unless they have withdrawn their consent to participate in any study related assessments.

[3] Except scheduled visit days.

[4] Optional Pre-screen consent to perform ELISA.

[5]To be assessed if it is an on-site or home visit.

[6] Assessments applicable for telephonic visits will be based on symptoms. Only those symptoms will be captured in relevant case report forms.

[7] For subjects with QTcF≥ 450 msec <480 msec at baseline or for subjects taking drugs which are CYP1A2 modulators, additional ECG monitoring will be performed at 4-5 hours after the first dose and 4 to 12 hours after the second dose.

[8] Stool Examination includes Rapid Sedimentation Technique (TSR) test and Kato-Katz test for parasitic load through egg count. Kato-Katz test to be performed only when Rapid Sedimentation Technique (TSR) test is positive.

Period	**Screening****		**Treatment**	**Follow up**									**Unscheduled**
Visit Name	**Pre-screening**	**Screening/Baseline**	**Treatment**	**FUP 1#**	**FUP 2#**	**FUP 3**	**FUP 4[1]**	**FUP 5**	**FUP 6[1]**	**FUP 7**	**FUP 8[1]**	**End of Study[2]**	**Unscheduled[3]**
Days	**-14**	**-2 to 1**	**1 to 2**	**3 ±1**	**6 ±1**	**10 ±1**	**15 ±2**	**30 ±3**	**45 ±5**	**60 ±5**	**75 ±5**	**90 ±5**	**2 to 90**

[9] Two stool samples are to be collected. Both can be collected up to 2 days before the visit or the second sample may be collected on the day of visit in clinic. Stool sample collected prior to the visit to be assessed first for Rapid sedimentation technique (TSR) and if TSR is positive then Kato-Katz test need to be done using the same stool sample. If TSR is negative for first stool sample, the assessment should be repeated as above for the second sample collected.
[10] As per physician discretion.
[11] Two doses of 10mg/kg given approximately 12 hours apart. Second dose can be home administration, except for patients for whom ECG is required.
[12] ELISA test conducted to detect presence of Fasciola. No need to repeat at screening/baseline visit if done as part of prescreen assessment or as per routine local practice. (Assessment must be complete within defined window).
[13] ALT, AST, ALP, Bilirubin (Total, Direct and Indirect), PT/INR, Albumin and GGT. Additional tests may be required (refer to Table 16-2) based on investigator discretion.
[14] A blood sample of 5-10 ml is required to conduct liver function tests, biochemistry and hematology tests or as per local laboratory requirements.
[15] Hemoglobin, Eosinophil count and Erythrocyte sedimentation rate (ESR) as applicable.
[16] Sodium, potassium, magnesium and calcium to be measured at screening
[17] Obtain only for females of child-bearing potential at screening.

8.1 Screening

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. The reason for screen failure should be entered on the applicable CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see SAE Section 10.1.3 for reporting details).

Subjects who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered as premature termination. The reason for premature termination should be captured on the appropriate disposition CRF.

It is permissible to re-screen a participant if she/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

8.2 Subject demographics/other baseline characteristics

It is recommended that the following data elements be collected (or recorded if already part of subject outpatient record) at baseline:

1) Subject demographics (age, sex, race, ethnicity)

2) Past history of fascioliasis and past treatments administered with triclabendazole/other drugs for the management of fascioliasis.

3) Fascioliasis diagnosis:

- Date fascioliasis diagnosis was established, including the diagnosis of acute or chronic type of infection
- Mode of diagnosis is based on the following parameters which are described in detail in (Section 1.1).
- Clinical symptoms - The disease presents with many specific and non-specific clinical symptoms as described in the (Section 1.1) of this protocol
- Laboratory tests - Involves assessment for eosinophilia, LFT, serological assessment (ELISA), stool tests for detection of eggs in feces (TSR and Kato-Katz tests)
- Imaging- Ultrasound to assess liver involvement
- Residence in endemic area

4) Relevant medical history/current medical conditions present before signing informed consent and any adverse events after signing informed consent.

5) Height and weight (for Body Mass Index (BMI) derivation).

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

8.3 Efficacy

Efficacy assessments will consist of clinical signs and symptoms, lab tests, ultrasound and stool examination. These assessments will be performed as per assessment schedule (Table 8-1).

Acute Fascioliasis

Clinical response (improvement or resolution of signs and symptoms) on Day 10 and clinical cure onDay 30, Day 60 and Day 90 which takes into consideration resolution of baseline clinical signs and symptoms, improvement in baseline lab parameters and improvement in baseline ultrasound findings of Fascioliasis. The efficacy assessments performed in Acute Fascioliasis patients are listed in Table 8-2.

Table 8-2 Efficacy Assessments for Acute Fascioliasis Patients

Clinical signs and symptoms*	Fever Abdominal pain Gastrointestinal disturbances (loss of appetite, flatulence, nausea, diarrhea) Urticaria
Ultrasonography	Abdomen – for hepatic lesions and/or biliary tract blockage caused by Fasciola worm(s).
Hematology	Eosinophil count

* Patients with acute stage fascioliasis may present with other symptoms not listed in the table and they will be captured by Investigator in respective CRF page.

Chronic fascioliasis

Clinical response (improvement or resolution of signs and symptoms) on Day 10 and clinical cure on Day 30, Day 60 and Day 90 which takes into consideration resolution of baseline clinical signs and symptoms, improvement in baseline lab parameters and improvement in baseline ultrasound findings of Fascioliasis. The efficacy assessments performed in Chronic Fascioliasis patients are listed in Table 8-3.

Table 8-3 Efficacy Assessments for Chronic Fascioliasis patients

Clinical signs and symptoms*	Fever Abdominal pain Gastrointestinal disturbances (loss of appetite, flatulence, nausea, diarrhea) Urticaria Ascites Jaundice Hepatomegaly Anemia
Ultrasonography	Abdomen – for hepatic lesions and/or biliary tract blockage caused by Fasciola worm(s).
Hematology and biochemistry	Hemoglobin Eosinophil count Erythrocyte sedimentation rate (ESR) Liver function test (ALT, AST, ALP, Bilirubin (Total, Direct and Indirect))

* Patients with chronic stage fascioliasis may present with other symptoms not listed in the table and they will be captured by Investigator in respective CRF page.

Parasitologic cure 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 (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. Further details are provided in Section 16.2: Stool assessments.

Treatment failures

Treatment failures 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 will be carried forward as the treatment failures. (Lumbreras et al 1962, Katz et al 1972, Resolucion Ministerial 2019)

8.3.1 Appropriateness of efficacy assessments

The study will be conducted in countries where Fascioliasis is endemic and the efficacy assessments take in to account the national/local treatment guidelines and the approved label of Egaten by US FDA. The intent is to have the study follow real world practices for diagnosis and follow-up, as far as possible.

8.4 Safety

Evaluation of all AEs and SAEs, Physical examination, Vital signs, and Laboratory assessments (Hematology, Liver function test, Biochemistry, Stool test) will be conducted as part of safety assessments.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. For details on AE collection and reporting, refer to AE (Section 10.1.1).

Table 8-4 Assessments & Specifications

Assessment	Specification
Physical examination	Disease focused and based on subject's symptoms. Information for all physical examinations must be included in the source documentation at the study site system. Significant findings that are present before signing the Informed consent form (ICF) must be included in the relevant medical history eCRF page. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event section of the eCRF.
Vital signs (Baseline)	Vital signs include Blood Pressure (BP) and pulse measurements.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate.

Table 8-5 List of laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Eosinophil/Leucocytes and Eosinophil count, Erythrocyte sedimentation rate (ESR)
Liver Function Test	Alkaline phosphatase, ALT , AST, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, PT/INR, Albumin and GGT
Biochemistry	Sodium,Potassium, Magnesium & Calcium

8.4.2 Electrocardiogram

Electrocardiograms (ECGs) must be recorded after 10 minutes' rest in the supine position to ensure a stable baseline. The Fridericia QT correction formula (QTcF) should be used for clinical decisions. ECG will be performed at screening to assess eligibility for study participation. Additional ECG monitoring at 4-5 hours after first dose and at 4 to 12 hours after the second dose for any of the following:

- Subjects with QTcF $\geq$ 450 msec, < 480 msec at screening.
- Subjects taking medications which are CYP1A2 modulators

Table 8-6 ECG collection plan for subset of patients monitored with ECG assessments

Day	Time	Number of ECG Replicates
-2 to 1	Pre-dose (screening ECG)	12 Lead Triplicate
1	4-5 hours Post-dose 1	12 Lead Triplicate
2	4- 12 hours Post-dose 2	12 Lead Triplicate
Unscheduled	Anytime	12 Lead Triplicate

ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

8.4.3 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

8.5.1 Trial Feedback

'Trial Feedback Questionnaire' may be used for subjects to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses would be used by the Novartis to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events and therefore would not be trial data. Should any spontaneous information be collected about AEs, this would be transferred to the safety database.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances

- Subject/guardian decision
- Any situation in which study participation might result in a safety risk to the subject
- QTcF $\geq$ 500 msec or increase of QTcF $\geq$ 30 msec from baseline in the ECG at 4-5 hours after first dose

If discontinuation from study treatment occurs due to subject/guardian decision, the investigator should make a reasonable effort to understand the primary reason for the subject's discontinuation from study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). Where possible, they should return for the assessments indicated in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

Subjects who have received rescue medication, would be considered treatment failures. They will be managed as per local treatment guidelines and will be followed up for the safety evaluation until Day 90 of the study.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, the following data should be collected at clinic visits or via telephone/email contact:

- Adverse Events / Serious Adverse Events
- New / concomitant treatments

9.1.2 Withdrawal of informed consent/ Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment and the safety follow up period must be completed.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The

investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their study completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

For participants whose disease status is unknown and who sign the pre-screening ICF, AEs which occur after the signature of this consent will only be captured if they meet the definition of serious as outlined in Section 10.1.2 and are reported to be causally related with study procedures. Once the main study ICF is signed, all AEs per the descriptions below will be captured as adverse events.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments. In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred. In addition, all reports of intentional misuse and abuse of the product are also considered as adverse event irrespective if a clinical event has occurred.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity of the adverse events can be graded as below:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken with study treatment may include one or more of the following:
   - Dose not changed
   - Drug interrupted/withdrawn
6. Its outcome, such as - not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until the end of study visit.

Information about adverse drug reactions for the investigational drug can be found in the prescribing information.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values, which are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

Information related to side effects will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between PI updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the end of study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Information about all SAEs is collected and recorded on the eSAE form with paper backup Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the prescribing information (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (CMO & PS) department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence irrespective of the fact whether any adverse events has occurred/reported or not. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Lactating women should discontinue lactation up to 72 hours after the second dose administration or as per local guidelines.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment

of the possible relationship to the study drug to any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Advise subjects that EGATEN should be taken orally with food. The tablets can be swallowed whole or, divided in half and taken with water, or crushed and administered with apple sauce. The crushed tablet mixed with apple sauce is stable for up to 4 hours.

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

AE – adverse event; eCRF – electronic case report form; SAE – serious adverse event

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

One of the key risk with the study drug is abdominal pain (characterized as biliary colic) and elevation of serum levels of some hepatic enzymes because of expulsion of dead or damaged flukes from the biliary tract, usually occurring during the first 10 days after treatment.

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 16-1 in Appendices 16 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, Total Bilirubin (TBL), Prothrombin time and International Normalized Ratio (PT/INR), Alkaline Phosphatase (ALP) and Gamma-Glutamyl Transferase (G-GT) to confirm elevation as per local practice guidelines.

- These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the subject should be initiated by Investigator, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Cardiac safety monitoring

Triclabendazole has been reported to cause QTc prolongation in a healthy human volunteer study.

The peak placebo-corrected mean increase from baseline was 9.2 msec with the therapeutic dose (2 doses of 10 mg/kg given 12 hours apart). Due to QT prolongation, there is a potential risk for Torsades de Pointes (TdP) with triclabendazole in patients with other risk factors for QT prolongation.

To ensure patient safety, patients with QTcF $\geq$ 450 msec - < 480 msec or patients taking drugs which are CYP1A2 modulators at screening will be monitored with additional ECG assessments as mentioned in Section 8.4.2. In addition, all patients will be followed up for any adverse events including events possibly related to cardiac arrhythmias as per the schedule given in Table 8-1.

In cases with an adverse event relating to cardiac arrhythmia or with post-dose QTcF ≥ 500 msec or increase of QTcF ≥ 30 msec from baseline in the ECG at 4-5 hour after first dose :

- Close observation of the subject should be initiated by Investigator
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the event
- Thorough follow-up and management of the adverse event as deemed appropriate by the Investigator.

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to Title 21 of Code of Federal Regulations (21 CFR) Part 11 requirements, Investigator site staff will not be given access to the electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis (or designated CRO) personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis or delegated CRO representative will review the protocol and data capture requirements (i.e. eSource direct data entry (DDE) or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis or delegated CRO, Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECG, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

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.

12.1 Analysis sets

The Full Analysis Set (FAS) includes all subjects who enrolled in the study and Safety set (SAF) includes enrolled subjects who received at least one dose of study treatment.

12.2 Subject demographics and other baseline characteristics

Demographic data and baseline disease characteristics will be descriptively presented and tabulated (n, mean, standard deviation, 25th percentile, median, 75th percentile, minimum, and maximum for continuous variables; n and percent for categorical variables) using the FAS.

12.3 Treatments

The number and percentage of subjects receiving treatment (one and/or two doses) will be presented.

The number and percentage of subjects receiving prior and concomitant medications will be summarized in SAF.

12.4 Analysis of the primary endpoint(s)

The primary analysis will be based on summary statistics on Safety set (SAF) population.

12.4.1 Definition of primary endpoint(s)

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/ (low and high).

12.4.2 Statistical model, hypothesis, and method of analysis

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

12.4.3 Handling of missing values/censoring/discontinuations

Missing or partially missing dates (year, month or day missing) will be handled using standard Novartis conventions, which will be detailed in the statistical analysis plan.

12.4.4 Sensitivity and Supportive analyses

No sensitivity analyses will be performed for the primary safety variables. Potential exploratory assessment in subgroups (such as age, gender, and race) for primary endpoints will be specified in the detailed statistical analysis plan.

12.5 Analysis of secondary endpoints

The analyses for secondary endpoints are mainly descriptive and no statistical comparison between visits will be performed.

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

The clinical cure rate in acute fascioliasis and chronic fascioliasis patients on Day 30, 60 and 90 will be presented separately for each of the following criteria (Table 8-2 and Table 8-3) as well as all criteria combined.

- Resolution of baseline signs and symptoms
- Improvement in baseline lab parameters
- Improvement in baseline ultrasound findings

The parasitological cure rate of chronic fascioliasis patients at Day 10, Day 30, Day 60 and Day 90 will also be provided.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

For secondary endpoints, the proportion and confidence interval (CI) of subjects who are clinical cures and/or parasitological cures for acute and chronic fascioliasis as defined in Section 8.3 will be presented by visit.

12.5.2 Safety endpoints

In addition to adverse event and laboratory assessments, descriptive statistics for vital signs will be provided for values and change from baseline at each assessment time point based on SAF.

12.5.3 Pharmacokinetics

Not applicable.

12.5.4 DNA

Not applicable.

12.5.5 Biomarkers

Not applicable.

12.5.6 PK/PD relationships

Not applicable.

12.5.7 Patient reported outcomes

Not applicable.

12.6 Analysis of exploratory endpoints

Not applicable.

12.7 Interim analyses

No interim analysis is planned for the study.

12.8 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.

12.8.1 Primary endpoint(s)

The sample size is based on the "rule of three". The power is not assessed for primary endpoint.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis/Novartis designated external monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (study last subject last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.) .

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

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

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal standard operating procedures (SOPs), and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants.

- Thank You letter.
- Plain language trial summary – after clinical study report publication.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN
	• ALP > 2 × ULN (in the absence of known bone pathology)
	• TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	• ALT or AST > 3 × ULN and INR > 1.5
	• Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	• Any clinical event of jaundice (or equivalent term)
	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	• Any adverse event potentially indicative of a liver toxicity*
*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious and infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal	

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency and laboratory parameters are at investigator discretion)

Criteria	Actions required	Follow-up monitoring
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency and laboratory parameters are at investigator discretion)
> 3 × ULN	• Continuation of the study treatment will be at investigator discretion • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency and laboratory parameters are at investigator discretion)
> 5 to ≤ 8 × ULN	• Continuation of the study treatment will be at as per investigator discretion • Repeat LFT within 48 hours or later based on investigator discretion • If elevation persists, continue follow-up monitoring • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency and laboratory parameters are at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Continuation of the study treatment will be at as per investigator discretion • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g.	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency and laboratory parameters are investigator discretion)

Criteria	Actions required	Follow-up monitoring
	conmeds, med hx, lab) in the appropriate CRF	
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week or later based on Investigator discretion • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours or later based on investigators discretion • If elevation persists, establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours or later based on investigator discretion • If elevation persists, continuation of the study treatment will be at as per investigator discretion • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency and laboratory parameters are at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin) as approriate as per investigator
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week or later based on investigator discretion • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Continuation of the study treatment will be at as per investigator discretion • Hospitalize the subject if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency and laboratory parameters are at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	
Any AE potentially indicative of a liver toxicity*	• Continuation of the study treatment will be at as per investigator discretion • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion
[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.		

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.2 Appendix 2: Stool assessments

Rapid sedimentation technique (TSR) described by Lumbreras:

Test used for detection of higher density of Fasciola eggs from feces sample. This concentration method helps identify Fasciola eggs in feces with a sensitivity of 98.5% and specificity of 100% (Lumbreras et al 1962, Resolucion Ministerial 2019).

Suggestive procedure for conducting the test is describe below:

- Homogenize 4-8 g of feces with 10-20 mL of filtered water.
- Transfer mixture to a container with a capacity of 200-300 mi, preferably conical, sieving it with a strainer covered by one or two layers of gauze.
- Fill up the volume with water and leave to stand for 20 minutes.
- Decant 2/3 of the supernatant and replenish the volume with more running water. Repeat the same until the supernatant comes out clean, at intervals of 5 minutes.
- Pour the last sediment into a petri dish or watch glass. Observe in the microscope or stereoscope.

Kato-Katz technique:

The test helps quantify the presence of Fasciola eggs in feces. The results are expressed in numbers of eggs per gram of stool (hpd). The procedure described the methodology for preparing the fecal sample slide and examining it under microscope. The number of eggs found on the slide are multiplied by a factor K (K=24) and the resulting number denotes the number of eggs per gram of stool (hph). This helps grade the level of parasitic load in the subject. For loose or soft stool a fact of "K/2" is applied and for diarrheic stool a factor of "K/3" is applied (Katz et al 1972, Resolucion Ministerial 2019).

Suggestive procedure for conducting the test is describe below:

- With an applicator (e.g., tongue depressor) transfer the stool sample (0.5 – 1 g) onto absorbent paper.
- Place a 2x3 cm mesh or nylon on the sample.
- With the applicator, compress the mesh to sieve the sample.
- Place the plastic mold with a 6 mm diameter central perforation on a slide and fill the perforation with the sieved sample.
- Lift the mold leaving the “cylinder” of the sample on the slide.
- Place a glycerinated slide with malachite green on the sample and with the help of a rubber stopper press on the slide, seeking to spread out the sample.
- Leave it at room temperature for 30 to 45 minutes.
- Examine the slide microscopically (100x, 400x)