Clinical Study Protocol

A Randomised, Double-Blind, Placebo-Controlled, Exploratory Phase I Trial Assessing the Pharmacokinetic Profile, Safety and Tolerability of a Continuous Daily Dosing Regimen of Ivermectin in Healthy Volunteers

Investigational Medicinal Product: Ivermectin

Sponsor Reference: [redacted]
MAC Number: [redacted]
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Clinical Development Phase: I

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For and on behalf of the Study Sponsor:

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DFBBC09D8B7B4DD...

Date: ..... [redacted]

[redacted]

INVESTIGATOR SIGNATURE PAGE

The undersigned confirm that the following Protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the study in compliance with the approved Protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical study without the prior written consent of the Sponsor.

I also confirm that I will, when required by the Sponsor, make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be provided; and that any discrepancies and serious breaches of GCP from the study as planned in this Protocol will be explained.

Principal Investigator:

Signature: [redacted]

SUMMARY OF CHANGES: CLINICAL STUDY PROTOCOL AMENDMENT 1 (VERSION 2.0)

This version of the protocol will supersede the previous version (Version 1.0, dated 27 August 2020).

The rationale for this non-substantial amendment is to reduce the frequency of fundoscopy assessments performed during the study, and to only perform this procedure following receipt of a recent negative test for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This is to reduce the risk of exposure to SARS-CoV-2 in the current pandemic for the subject and the study team member performing the assessment, due to their close proximity when performing this procedure. The time window for pre-dose 12-lead ECG assessments has also been extended to 2 hours, to align with MAC Clinical Research Standard Operating Procedures.

The changes to the protocol are detailed below:

Section	Description of Change
Section 5.2 (Page 30) – Dose Administration (Table 4 footnote)	**Previous text:** Not applicable. **Amended text:** Non-whole weight values will be rounded to the nearest whole number. For example, 95.1 to 95.4 kg would be rounded down to 95 kg and 95.5 to 95.9 kg would be rounded up to 96 kg.
Section 7.2 (Page 38) – 12-lead Electrocardiogram	**Previous text:** The 12-lead ECG will be collected in triplicate, approximately 1 minute apart, at Screening, Day -1 and within approximately 1 hour pre-dose on Day 1. **Amended text:** The 12-lead ECG will be collected in triplicate, approximately 1 minute apart, at Screening, Day -1 and within ~~approximately 1 hour~~ 2 hours pre-dose on Day 1.
Section 11.1 (Page 49) – Randomisation and Subject Allocation	**Previous text:** The randomisation number will have 4 digital numbers, with the first being the cohort (i.e., 1 for Cohort 1, 2 for Cohort 2, etc), the second being whether a subject is a replacement (0 = original; 1 = replacement), and the last 2 being the subject number from 01 to 24; for example, 1011 means the 11th subject in the originally randomised Cohort 1, whereas 1111 is the replacement of 1011. All screened subjects should be identifiable throughout the study. **Amended text:** The randomisation number will have 4 digital numbers, with the first being the cohort (i.e., 1 for Cohort 1, 2 for Cohort 2, etc), the second being whether a subject is a replacement (0 = original; 1 = replacement), and the last 2 being the subject number ~~from 01 to 24~~; for example, ~~1011~~1001 means the ~~11th~~1st subject in the originally randomised Cohort 1, whereas ~~1111~~1101 is the replacement of ~~1011~~1001. All screened subjects should be identifiable throughout the study.

Strikethrough text indicates deletions. Underlined text indicates additions.

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SYNOPSIS

Study Title: A Randomised, Double-Blind, Placebo-Controlled, Exploratory Phase I Trial Assessing the Pharmacokinetic Profile, Safety and Tolerability of a Continuous Daily Dosing Regimen of Ivermectin in Healthy Volunteers

Investigational Medicinal Product: Ivermectin

Clinical Phase: I

Objectives:

The primary objective of this study is to characterise the pharmacokinetic (PK) profile of ivermectin following daily repeated doses for 28 days.

The secondary objective of this study is to characterise the safety and tolerability profile of daily repeated dosing of ivermectin for 28 days.

The exploratory objective of the study is to evaluate the potential of ivermectin as a prophylactic measure to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection.

Endpoints:

The primary endpoints of the study are plasma PK concentrations including but not limited to: maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), [redacted] area under the plasma concentration-time curve from zero to 24 hours (AUC_{0-24h}), [redacted] and apparent terminal half-life ($t_{1/2}$).

The secondary endpoint of the study is the clinical safety data from adverse event (AE) reporting, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory evaluations, and physical and neurological examinations in healthy male subjects.

The exploratory endpoint of the study is the occurrence of SARS-CoV-2 infection as confirmed by reverse transcription polymerase chain reaction (RT-PCR) test and/or serology.

Study Design:

This is a Phase I, double-blind, placebo-controlled, randomised study to determine the PK profile, safety and tolerability of multiple oral doses of ivermectin.

Up to 24 subjects are planned to be enrolled into 3 cohorts comprising 8 subjects each. In each cohort, 6 subjects will be randomised to receive ivermectin and 2 subjects will be randomised to receive placebo. Multiple-dose oral administration of once daily ivermectin or placebo will occur for 28 days. All cohorts will consist of 2 sentinel subjects, of whom 1 subject will receive ivermectin and 1 subject will receive matched placebo. The remaining subjects in each cohort (6 subjects; 5 subjects ivermectin and 1 subject placebo) will commence treatment after satisfactory review of the safety data up to a minimum of 4 hours post-dose on Day 7 from the sentinel subjects, if deemed safe to do so by the Principal Investigator.

Up to 3 dose levels are planned. The dose levels will be administered in an ascending order; progression to the next dose level, and dose selection, will be based on the safety, tolerability and available PK data from the preceding dose cohort(s) (safety, tolerability and PK data [up to Day 14] from a minimum of 4 ivermectin and 1 placebo subjects in the preceding dose cohort). Except for the starting dose, the doses outlined in the protocol are preliminary, with actual subsequent doses determined based on an ongoing evaluation of the safety, tolerability, and PK data by the Safety Review Committee (SRC)

Subjects will be required to attend the Clinical Research Unit (CRU) for a Screening visit within 28 days prior to first dosing to ensure they meet the inclusion/exclusion criteria and are in good health. Subjects will be admitted to the CRU 1 day prior to first dosing (Day -1) for collection of baseline safety assessments and will receive their first dose of ivermectin or placebo in the morning of Day 1, following an overnight fast.

Subsequent daily doses of ivermectin or placebo will be administered in the morning in the CRU from Day 2 to Day 7, following an overnight fast. Subjects will reside in the CRU until at least 4 hours post-dose on Day 7 for the collection of safety assessments and PK blood samples but may reside for longer if deemed necessary by the Investigator. From Day 8 to Day 27, subjects will self-administer their daily dose of ivermectin or placebo at home following an overnight fast, with the exception of outpatient visits on Day 14 and Day 21 which will be administered in the CRU. Subjects will be readmitted to the CRU on Day 28 to receive their final dose of ivermectin or placebo and will be discharged on Day 29 following safety assessments and PK blood samples. Subjects will return to the CRU for outpatient visits on Days 32, 35 and 42 for safety assessments and PK blood samples.

Treatment Duration: Once daily dosing for 28 days

Study Participants:

Healthy male subjects, with a body mass index of 18.5 to 32.0 kg/m^2 (inclusive), of any ethic origin. Subjects should be aged between 18 to 45 years, inclusive.

Dose and Route of Administration:

The ivermectin or matched placebo will be orally administered in the morning from Day 1 to Day 28 following an overnight fast. Each dose will be taken with 240 mL of water at room temperature. Water will be allowed ad libitum and breakfast can be eaten between 1 to 2 hours after dosing.

The planned dose levels are presented in the table below.

Cohort 1	Loading dose of 200 µg/kg on Day 1, then 50 µg/kg/day from Day 2 to Day 28
Cohort 2	Loading dose of 200 µg/kg on Day 1, then 75 µg/kg/day from Day 2 to Day 28
Cohort 3	Loading dose of 200 µg/kg on Day 1, then 100 µg/kg/day from Day 2 to Day 28

Criteria for Evaluation:

Pharmacokinetics will be assessed by blood sampling. Safety will be assessed through AE reporting, 12-lead ECG, vital signs, physical examinations, comprehensive neurological examinations and clinical laboratory evaluations. Efficacy will be assessed through the occurrence of SARS-CoV-2 infection, as confirmed by serology.

Statistical Analysis:

Pharmacokinetic parameters will be derived from individual plasma concentration data of ivermectin by noncompartmental analysis. The PK parameters derived to assess the multiple dose PK of ivermectin are provided below.

Abbreviation	Definition
C_{max}	Maximum plasma concentration
[redacted]	[redacted]
t_{max}	Time of maximum plasma concentration
AUC_{0-24h}	Area under the plasma concentration-time curve from zero to 24 hours
[redacted]	[redacted]
[redacted]	[redacted]
$t_{1/2}$	Apparent terminal half-life
RA	Accumulation ratio

Steady state will be assessed from visual examination of the data. In addition, dose proportionality will be determined using a suitable statistical model.

Safety and efficacy parameters will be listed and summarised using descriptive statistics.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-24h}	area under the plasma concentration-time curve from zero to 24 hours
[redacted]	[redacted]
BMI	body mass index
[redacted]	[redacted]
CDC	Centers for Disease Control and Prevention
C_{max}	maximum plasma concentration
COVID-19	Coronavirus Disease 2019
CRU	Clinical Research Unit
[redacted]	[redacted]
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
FAS	Full Analysis Set
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	anti-hepatitis C antibody
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IgM	immunoglobulin
IMP	Investigational Medicinal Product
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NOAEL	no observed-adverse-effect level

OTC	over-the-counter
PK	pharmacokinetic(s)
PT	preferred term
PV	Pharmacovigilance Vendor
RA	accumulation ratio
REC	research ethics committee
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SOC	system-organ class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
$t_{1/2}$	apparent terminal half-life
t_{max}	time to reach the maximum plasma concentration
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

1.1. Background and Study Rationale

Coronavirus Disease 2019 (COVID-19) is a highly contagious disease, caused by a novel enveloped RNA beta-coronavirus, also known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Following an initial outbreak in the Chinese city of Wuhan at the end of 2019, it became a pandemic, with more than 21.2 million cases and 761 000 deaths reported worldwide as of August 16 2020.[1] Since its isolation and identification in January 2020, the exact pathogenic mechanism(s) of this virus is (are) to be clearly established. While the majority of patients with COVID-19 develop mild or uncomplicated illness, approximately 20% to 30% of hospitalised patients have required intensive care support and 5% of those have multi-organ failure or shock. The case fatality rate ranges from 1% to 4% and it is higher among those with pre-existing comorbid conditions. To date, treatments for COVID-19 in high risk individuals remain experimental and therapeutic strategies to deal with the infection are at best supportive, with prevention aimed at reducing transmission in the community as the best strategy.

Despite its apparent low lethality (<2%), its high infectivity and fast spread has prompted the repurposing of existing drugs developed for other indications. These drugs may have a specific antiviral activity (antiviral agents) and/or can be host-targeted agents meaning that they impact host specific targets playing a role in the SARS-CoV-2 infectivity or in the COVID-19 physiopathology.[2]

1.2. Ivermectin

Ivermectin tablets will be the study drug to be administered to healthy volunteers in this study in the context of the development of a product containing ivermectin for pre-exposure prophylaxis against SARS-CoV-2 infection.

Ivermectin is a drug that is well known in Africa and Latin America and some experts regard it as one of the greatest health interventions of the past 50 years. It is used to treat a variety of internal nematode infection including Onchocerciasis, Strongyloidiasis, Ascariasis, cutaneous larva migrans, filariases, Gnathosto-miasis and Trichuriasis, as well as for oral treatment of ectoparasitic infections, such as Pediculosis (lice infestation) and scabies (mite infestation). Alongside penicillin and aspirin, it lays claim to the title of 'Wonder drug', based on its versatility, safety and the beneficial impact that it has had, and continues to have. It was initially commercialised for multi-purpose use in animal health in 1981 as it kills a wide range of internal and external parasites in commercial livestock and companion animals. It was quickly discovered to be ideal in combating two of the world's most devastating and disfiguring diseases, Onchocerciasis and Lymphatic filariasis, and 6 years later it was registered for human use. It is now being used free-of-charge as the sole tool in campaigns to eliminate both diseases globally.[3] New roles in other human diseases, including the management SARS-CoV-2, are continually being found.[4]

Ivermectin causes death of parasites, primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The selective activity of compounds of this class is attributable to the fact that some mammals do not have

glutamate-gated chloride channels, that avermectins have a low affinity for mammalian ligand-gated chloride channels, and that they do not readily cross the blood-brain barrier in humans.

Recently, ivermectin has been shown to be a potent inhibitor of Importin α/β-mediated nuclear transport and exhibits antiviral activity towards several RNA and DNA viruses by blocking the nuclear trafficking of viral proteins.[5,6,7,8] In Flaviviruses, ivermectin was also shown to inhibit the viral helicase, a key enzyme involved in viral replication that has also been identified in SARS-CoV-2.[9,10] The pharmacological mechanism may explain the inhibitory effect of ivermectin on the SARS-CoV-2 replication observed in vitro in Vero cells.[11] Several clinical trials are currently testing ivermectin as a treatment for COVID-19. By its actions on Importin α/β and on viral helicase, ivermectin may present a combined antiviral and host-targeted effect against SARS-CoV-2, and its wide use and clearly established safety profile justify further clinical investigations as a possible treatment against COVID-19.

The aim of this study is to evaluate the safety, tolerability and pharmacokinetic (PK) profile of daily dosing of ivermectin for 28 days, using 3 different dosing regimens, as a potential long-term prophylaxis for COVID-19.

1.3. Non-Clinical Experience

1.3.1. Non-Clinical Pharmacology

In vitro, ivermectin has an antiviral action against the SARS-CoV-2 clinical isolate, with a single dose able to control viral replication within 24 to 48 hours in Vero cells (IC_{50}: ~2 μM).[11] Ivermectin may exert its antiviral activity through the direct inhibition of the nuclear transporter importin α/β, limiting the entry of key viral protein into the host's nucleus, as described with other RNA and DNA viruses.[5,6,7,8] Additionally, ivermectin has been shown to efficiently inhibit the flaviviral helicase, a non-structural protein essential for subsequent viral replication and proliferation that is also present in SARS-CoV-2.[9,10]

Safety pharmacology studies data originate from the New Drug Application (NDA) 206255 of Soolantra (Ivermectin).[12] In safety pharmacology studies, no treatment-related effects on spontaneous activity, central nervous system excitability, sensory, motor, autonomic or neuromuscular function or body temperature were noted in rats at single oral doses up to 5 mg/kg ivermectin. In a second study, a dose-dependent decrease in motor activity was noted at single oral doses of 7 and 20 mg/kg in rats (no observed-adverse-effect level [NOAEL]: 3 mg/kg). Single oral doses of ivermectin up to 20 mg/kg had no effects on intrinsic convulsive activity or pentylenetetrazole-induced convulsive activity and on intrinsic analgesic activity or pentobarbital-induced anaesthesia. Ivermectin had no significant effects on the delayed rectifier potassium current in an in vitro hERG assay at concentrations up to 10 μM. In conscious beagle dogs, single oral doses of ivermectin at 1.5 mg/kg was slightly hypotensive. Ivermectin reduced the gastrointestinal transit in rats at a single oral dose of 20 mg/kg and dose-dependently reduced gastric emptying from 7 mg/kg. Ivermectin at single oral doses up to 20 mg/kg had no significant effects on urinary volume, urinary pH, potassium, sodium, or creatinine excretion in rats.

1.3.2. Pharmacokinetics in Animals

Oral bioavailability of ivermectin is low in rats and dogs (25% to 41%). Ivermectin is widely distributed to tissues and no blood brain barrier passage is noted after either oral or intravenous administration in rats.[12,13] After administration to pregnant rats, transfer of ivermectin through the placenta is low and ivermectin was found to be quantitatively transferred to milk.

Ivermectin is highly bound to plasma proteins (99.9%) in mouse, rat, rabbit, dog, minipig and human, with low in vitro partitioning into red blood cells. The fraction of ivermectin that is metabolised is higher after oral administration indicating a hepatic first-pass effect. Demethylation and hydroxylation appear to be the main metabolic reactions and no significant gender differences in metabolism are noted in rats. Cytochrome P450 (CYP)3A4 was identified as the enzyme primarily responsible for the metabolism of ivermectin. CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared to CYP3A4. Ivermectin is slowly eliminated, the primary route of excretion being in the faeces. The majority of radioactivity associated with ivermectin is excreted within 48 hours after oral administration to rats.

1.3.3. Toxicology

Ivermectin appears to be neurotoxic at high oral doses, indicated by signs of mydriasis, tremors, and ataxia, presumably through an effect on GABA neurons.

In single dose oral toxicity studies, the signs of toxicity were ptosis, bradypnea, ataxia, tremors, and loss of the righting reflex (in rodents); mydriasis (in dogs [5 to 80 mg/kg studied]); vomiting (in monkeys [0.2 to 24 mg/kg studied]).

In repeat dose oral toxicity studies, enlarged spleens with extramedullary haematopoiesis and minimal decreased secretion in seminal vesicles was noted in rats (up to 12 mg/kg/day studied); salivation, mydriasis, anorexia, dehydration, tremors and ataxia were noted in dogs (0 to 2.5 mg/kg/day studied); no significant toxicities were noted in a study in immature monkeys (0 to 1.2 mg/kg/day studied) or in a study in neonatal monkeys (0 to 0.1 mg/kg/day studied).

Ivermectin is not genotoxic in the Ames test, mouse lymphoma assay, or in vivo rat micronucleus assay.

Carcinogenicity (hepatocellular adenoma) of ivermectin has been detected at high dose (9 mg/kg/day) in a 104-week study in rats. There were no significant test article-related neoplastic findings in males treated with 1 or 3 mg/kg/day ivermectin.

Ivermectin is teratogenic in mice, rats, and rabbits. Cleft palate, wavy ribs, and clubbed forepaws were seen in these studies. The teratogenic effects were found at or near oral doses that produced maternal toxicity.

Further details regarding the preclinical data can be found in the Investigator Brochure (IB).

1.4. Clinical Experience

Ivermectin is a potent anthelminthic drug with a good and well described safety profile. Ivermectin has been used in clinical practice for over 30 years, since 1987 with an estimated 1.3 billion treatments for river blindness.[14] This good safety profile may be attributed to its high affinity to invertebrate neuronal glutamate-coupled chloride channels and its inability to cross the blood–brain barrier in humans and other mammals.[15] In addition, ivermectin has been administered to healthy patients at doses 7 to 10 times the maximum approved therapeutic dose, with no severe adverse events (AEs) being reported.[16,17]

Tolerance to the compound has been assessed in healthy volunteers and in patients; adverse effects are usually mild and transient. but their severity may be increased in patients infected with more than one parasite, particularly in the case of infestation with Loa loa.

Following oral administration of ivermectin to healthy volunteers, plasma concentrations are relatively proportional to the dose level in the 30 to 120 mg dose range (i.e., 333-2000 µg/kg).[16]

The mean peak plasma concentration of the major component (H2B1a), observed approximately 4 hours after oral administration of a single 12 mg dose of ivermectin in tablet form is 46.6 (± 21.9) ng/mL. Ivermectin plasma concentration increases with increasing doses in a generally proportional manner. Ivermectin is absorbed and metabolised in the human body and ivermectin and/or its metabolites are excreted almost exclusively in faeces, whilst less than 1% of the administered dose is excreted in urine.[18] The plasma half-life of ivermectin is about 12 hours (range in human healthy volunteers: 11.1 to 36.6 hours) and that of the metabolites is about 3 days.

1.4.1. Clinical Experience from the Treatment of Strongyloidiasis

In 4 clinical studies[19] involving a total of 109 patients given either one or two doses of 170 to 200 µg/kg of ivermectin, the following AEs were reported as possibly, probably, or definitely related to ivermectin:

Body as a Whole: asthenia/fatigue (0.9%), abdominal pain (0.9%)

Gastrointestinal: anorexia (0.9%), constipation (0.9%), diarrhoea (1.8%), nausea (1.8%), vomiting (0.9%)

Nervous System/Psychiatric: dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%)

Skin: pruritus (2.8%), rash (0.9%), and urticaria (0.9%).

The following laboratory abnormalities were seen regardless of drug relationship:

Elevation in alanine aminotransferase (ALT) and/or aspartate aminotransferase AST (2%), decrease in leukocyte count (3%). Leukopenia and anaemia were seen in one patient.

In comparative trials, patients treated with ivermectin experienced more abdominal distention and chest discomfort than patients treated with albendazole. However, ivermectin was better tolerated than thiabendazole in comparative studies involving 37 patients treated with thiabendazole.

1.4.2. Clinical Experience from the Treatment of Onchocerciasis

In clinical trials[19] involving 963 adult patients treated with 100 to 200 µg /kg ivermectin, worsening of the following Mazzotti reactions during the first 4 days post-treatment were reported: arthralgia/synovitis (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively), cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively), inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), other lymph node enlargement and tenderness (3.0% and 1.9%, respectively), pruritus (27.5%), skin involvement including oedema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%).

Ophthalmological conditions were examined before treatment, at Day 3, and months 3 and 6 after treatment with 100 to 200 µg /kg ivermectin. Changes observed were primarily deterioration from baseline 3 days post-treatment. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at Day 3, month 3 and 6, respectively, were: limbitis: 5.5%, 4.8%, and 3.5% and punctate opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis: 6.2%, 9.9%, and 9.4% and punctate opacity: 2.0%, 6.4%, and 7.2%.

The following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: facial oedema (1.2%), peripheral oedema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

A similar safety profile was observed in an open study in paediatric patients ages 6 to 13.

The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with ivermectin: abnormal sensation in the eyes, eyelid oedema, anterior uveitis, conjunctivitis, limbitis, keratitis, and chorioretinitis or choroiditis. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.

The following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: eosinophilia (3%) and haemoglobin increase (1%).

1.4.3. Post-Marketing Experience

Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin have been reported.[19] Conjunctival haemorrhage has been reported in the treatment of Onchocerciasis.

Further details regarding the clinical data can be found in the IB or the Summary of Product Characteristics.[19]

1.5. Risk/Benefit Assessment

Further information about the known and expected benefits and risks and reasonably expected AEs of ivermectin may be found in the current IB and the Summary of Product Characteristics.[19]

Details of these risks and the proposed strategy to mitigate/monitor these risks are detailed in Table 1.

In this study, safety will be monitored closely both by subjective reporting and by objective means i.e., serial assessments of vital signs, clinical laboratory evaluations data, physical examinations, 12-lead electrocardiogram (ECG) and comprehensive neurological examinations. This study will be run in a Clinical Research Unit (CRU) with immediate access to hospital facilities for the treatment of medical emergencies. Subjects will remain monitored in the clinic for the first 7 days of dosing and will only be discharged from the CRU at the end of Day 7 if the Investigator deems it safe to do so.

Table 1: Risk/Benefit Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Skin rashes and pruritus	SmPC	Physical examinations will be performed regularly throughout the study to identify any rashes and overall TEAEs will be monitored.
Cardiovascular changes	SmPC	Heart rate and blood pressure will be frequently monitored during the study by supine and standing vital signs.
CNS changes	SmPC	Comprehensive neurological examinations will occur frequently during the study to identify any changes.
Gastrointestinal system effects	SmPC	Clinical monitoring of body weight and standard safety laboratory parameters, as well as overall TEAEs will be monitored. Subjects will be withdrawn if effects are severe.
Respiratory system changes; exacerbation of asthma	SmPC	Asthmatic subjects will be excluded.
Ophthalmologic changes	SmPC; IB	Comprehensive neurological examinations will occur frequently during the study to identify any changes.
Haematological changes	SmPC	Subjects will be closely monitored with frequent blood tests during the study. Haematology parameters will be closely monitored throughout the course of the study as dose escalation proceeds. Escalation to higher doses and exposures will only occur if emerging data indicates this is safe and appropriate. Stopping criteria have been added for clinically significant lab results. If indicated, no further dose escalation will occur.
Liver dysfunction: elevation in ALT, AST and/or bilirubin; acute hepatitis.	SmPC	Subjects will be closely monitored with frequent blood tests during the study. Liver function test parameters must be entirely normal for study eligibility and no alcohol will be allowed from 48 hours prior to Day -1. Clinical chemistry parameters will be closely monitored throughout the course of the study as dose escalation proceeds. Escalation to higher doses and exposures will only occur if emerging data indicates this is safe and appropriate. Stopping criteria have

		been added for clinically significant lab results. If indicated, no further dose escalation will occur.
Drug-drug interaction	In pre-clinical studies, ivermectin has been shown to be most likely hepatically metabolised through the CYP3A4 system. In pre-clinical studies, a subpopulation of CF-1 mice with P-gp deficiency presented with a 10 to 100-fold increase in ivermectin sensitivity and increased concentration of ivermectin were found in the intestine and in the brain.	Concomitant medication restrictions; co-administration of ivermectin and drugs known to be CYP3A4 or P-gp substrates will be avoided.
Risk of local or systemic allergic response.	SmPC and risk from multiple dose accumulation	This study will be performed in a CRU equipped to deal with allergic responses and anaphylaxis with access to hospital emergency facilities, if needed. Sentinel subjects will be dosed in each cohort. During outpatient periods there will be close contact with the CRU to ensure any type of local or systemic reaction is highlighted.
Exposure to SARS-CoV-2	Exposure to other infections is always a risk when study subjects attend a clinical research facility, but increased risk due to SARS-CoV-2 pandemic.	A SARS-CoV-2 test (according to the current UK standard testing) screen will be performed at Screening and prior to any inpatient stays. Additional SARS-CoV-2 tests will be carried out, as required, if any subject displays any of the signs and symptoms. The subject's temperature will be taken at the start of every visit to help assess SARS-CoV-2 status. In addition to temperature checks, subjects will be asked SARS-CoV-2 standard questions prior to all visits to the CRU. The CRU has been in operation throughout the lockdown period and will continue to monitor the situation and adhere to current UK Government advice around social distancing and personal protective equipment to protect site staff and study subjects. The requirement for, and duration of, inpatient stays has been minimised where safely possible. Distancing is in place within the CRU to ensure the least amount of contact possible, with both staff and subjects wearing face coverings. Any communal areas have been put out

		of use with restrictions on use of bathrooms and showers to ensure safety.

Abbreviations: ALT – alanine aminotransferase; AST – aspartate aminotransferase; CNS – Central Nervous System; CRU – Clinical Research Unit; CYP – cytochrome P450; IB – Investigator Brochure; P-gp – P-glycoprotein; SARS-CoV-2 – severe acute respiratory syndrome coronavirus-2; SmPC – summary of product characteristics; TEAE – treatment emergent adverse event.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to characterise the PK profile of ivermectin following daily repeated doses for 28 days.

2.1.2. Secondary Objectives(s)

The secondary objective of this study is to characterise the safety and tolerability profile of daily repeated dosing of ivermectin for 28 days.

2.1.3. Exploratory Objective

The exploratory objective of this study is to evaluate the potential of ivermectin as a prophylactic measure to SARS-CoV-2 infection.

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoints of the study are plasma PK concentrations including but not limited to: maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), [redacted] area under the plasma concentration-time curve from zero to 24 hours (AUC_{0-24h}), [redacted] apparent terminal half-life ($t_{1/2}$).

2.2.2. Secondary Endpoint(s)

The secondary endpoint of the study is the clinical safety data from AE reporting, 12-lead ECG, vital signs, clinical laboratory evaluations, and physical and neurological examinations in healthy male subjects.

2.2.3. Exploratory Endpoints

The exploratory endpoint of the study is the occurrence of SARS-CoV-2 infection as confirmed by reverse transcription polymerase chain reaction (RT-PCR) test and/or serology.

3. STUDY DESIGN

This is a Phase I, double-blind, placebo-controlled, randomised study to determine the PK profile, safety and tolerability of multiple oral doses of ivermectin in healthy male subjects [redacted]

[redacted]

Up to 24 subjects are planned to be enrolled into 3 cohorts comprising 8 subjects each. In each cohort, 6 subjects will be randomised to receive ivermectin and 2 subjects will be randomised to receive placebo. Multiple-dose oral administration of once daily ivermectin or placebo will occur for 28 days. All cohorts will consist of 2 sentinel subjects, of whom 1 subject will receive ivermectin and 1 subject will receive matched placebo. The remaining subjects in each cohort (6 subjects; 5 subjects ivermectin and 1 subject placebo) will commence treatment after satisfactory review of the safety data up to a minimum of 4 hours post-dose on Day 7 from the sentinel subjects, if deemed safe to do so by the Principal Investigator.

The planned dose levels are presented in Table 2.

Table 2: Planned Dose Levels

Cohort 1	Loading dose of 200 µg/kg on Day 1, then 50 µg/kg/day from Day 2 to Day 28
Cohort 2	Loading dose of 200 µg/kg on Day 1, then 75 µg/kg/day from Day 2 to Day 28
Cohort 3	Loading dose of 200 µg/kg on Day 1, then 100 µg/kg/day from Day 2 to Day 28

The dose levels will be administered in an ascending order; progression to the next dose level, and dose selection, will be based on the safety, tolerability and available PK data from the preceding dose cohort(s) (safety, tolerability and PK data [up to Day 14] from a minimum of

4 ivermectin and 1 placebo subjects in the preceding dose cohort). Except for the starting dose, the doses outlined in the protocol are preliminary, with actual subsequent doses determined based on an ongoing evaluation of the safety, tolerability, and PK data by the Safety Review Committee (SRC; described in Section 3.2.1).

Subjects will be required to attend the CRU for a Screening visit within 28 days prior to first dosing to ensure they meet the inclusion/exclusion criteria and are in good health. Subjects will be admitted to the CRU 1 day prior to first dosing (Day -1) for collection of baseline safety assessments and will receive their first dose of ivermectin or placebo in the morning of Day 1, following an overnight fast. Subsequent daily doses of ivermectin or placebo will be administered in the morning in the CRU from Day 2 to Day 7, following an overnight fast. Subjects will reside in the CRU until at least 4 hours post-dose on Day 7 for the collection of safety assessments and PK blood samples but may reside for longer if deemed necessary by the Investigator. From Day 8 to Day 27, subjects will self-administer their daily dose of ivermectin or placebo at home following an overnight fast, with the exception of outpatient visits on Day 14 and Day 21 which will be administered in the CRU. Subjects will be readmitted to the CRU on Day 28 to receive their final dose of ivermectin or placebo and will be discharged on Day 29 following safety assessments and PK blood samples. Subjects will return to the CRU for outpatient visits on Days 32, 35 and 42 for safety assessments and PK blood samples.

A detailed plan of study assessments is provided in Appendix 1.

3.1. Rationale for Study Design

This study is designed to evaluate the PK profile, safety and tolerability of multiple (28-day) ascending doses of ivermectin in healthy male subjects. This information will help to establish the dose and regimen suitable for administration in future studies.

In line with the European Medicines Agency Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with Investigational Medicinal Products (IMPs)[20], all cohorts will consist of 2 sentinel subjects; 1 receiving ivermectin and 1 receiving placebo. The remaining 6 subjects in each cohort (5 receiving ivermectin and 1 receiving placebo) will be dosed only if safe to do so based on the safety data from up to a minimum of 4 hours post-dose on Day 7 from the sentinel subjects.

To mitigate risk to subjects in this study, the cohorts will be recruited sequentially with progression through the cohorts dependent on adequate safety and PK data from the previous cohort and approval by the SRC. The SRC findings at each review will be documented.

To ensure compliance with the dosing regimen whilst outside the CRU, subjects will be contacted regularly by phone or text message to ensure that the correct number of tablets are being taken, and that doses have been following an overnight fast.

Since the safety profile in humans over 28 days of consecutive dosing has not yet been investigated, all subjects will be closely monitored. Standard assessments to evaluate safety and tolerability, including vital signs, physical examinations, neurological examination, 12-lead ECGs, clinical laboratory evaluations and AE collection will be utilised in this study.

3.2. Dose Rationale

Ivermectin has been used in clinical practice for over 30 years, since 1987 with an estimated 1.3 billion treatments for river blindness.[14] The standard approved dose of 200 µg/kg is taken once to three times a year[14] but much higher doses, up to 2,000 µg/kg taken in split doses over

one week found ivermectin to be generally well tolerated, with no difference in AEs between placebo and these highest doses.[16] However, despite these high doses no study has investigated continuous daily dosing for one month which would have the potential for a prophylaxis treatment of COVID-19.

In healthy volunteers receiving oral doses of ivermectin up to 120 mg (equivalent to a dose per body weight of 1404 to 2000 µg/kg), the C_{max} was 247.8. ± 158.9 ng/ml with no significant increase in AEs recorded compared to the placebo treated group.[16] This value is equivalent to approximately 2.2 times the minimum mean C_{max} after 13 weeks of repeated daily oral treatment at the lowest NOAEL in rats and is similar to the lowest mean C_{max} after 13 weeks of repeated daily oral treatment at the NOAEL in dogs Table 3.

After 3 repeated administrations of 30 mg ivermectin three times in a week (equivalent to 347 to 594 µg/kg every fourth day or 149 to 232 µg/kg/day) in healthy volunteers, the mean C_{max} and $AUC_{0-\infty}$ were 87.0 ng/ml and 2819.4 ng.h/mL, respectively.[16] When compared to the animal data after 13 weeks daily oral treatments with ivermectin at the NOAELs, these values are 1.2 to 6.4 lower than the mean C_{max} values found in rats and dogs, and 2 times higher to 2 times lower than the mean AUC_{0-24h} values found in rats and dogs, respectively dogs Table 3.

Table 3: Summary of the Main Toxicokinetic Parameters from Selected Preclinical Studies and the corresponding HED at the NOAELs[12]

Study Type	Species	NOAEL	HED at the NOAEL	C_{max} at the NOAEL (ng/ml)		AUC_{0-24h} at the NOAEL (ng h/ml)		Dose Effect	Accumulation
				Males	Females	Males	Females		
13-weeks DRF study in rats	Wistar rats	1	161 µg/kg/day	Day 1: 81.6 Day 91: 128	Day 1: 91.5 Day 91: 112	Day 1: 1417 Day 91: 1629	Day 1: 1337 Day 91: 1431	More than dose proportional increase	Slight accumulation (dose ≥ 1mg/kg/day)
13-week oral toxicity study in rats	Wistar rats	3	484 µg/kg/day	Day 1: 417 Day 88: 558	Day 1: 367 Day 88: 508	Day 1: 4770 Day 88: 7786	Day 1: 4803 Day 88: 7470	More than dose proportional increase in the 1-3 mg/kg/day range	Slight accumulation
13-week oral toxicity study in dogs	Beagle dogs	0.5	278 µg/kg/day	Day 1: 195 Day 90: 365	Day 1: 209 Day 90: 282	Day 1: 2282 Day 90: 5629	Day 1: 2494 Day 90: 4166	Dose proportional increase in exposure at doses below the NOAEL	Accumulation

Abbreviations: AUC_{0-24h} – area under the plasma concentration-time curve from zero to 24 hours; C_{max} – maximum plasma concentration; DRF – dose range finding; HED – human equivalent dose; NOAEL – no observed-adverse-effect level.

In cases of severe crusted scabies, the Centers for Disease Control and Prevention (CDC) recommends a dosing regimen of 200 µg/kg up to 7 times for a 28-day period (dosing on Day 1, Day 2, Day 8, Day 9, Day 15, Day 22 and Day 28).[21] This gives a total dose per month of 1400 µg/kg. These recommendations are also endorsed by the European Academy of Dermatology and Venerology[22] as well as the Department of Health and Families of the Northern Territory Government of Australia.[23]

The proposed dosing regimen is over a 28-day period consisting of a first loading dose of 200 µg/kg for the first day followed by once daily dosing of either 50, 75 or 100 µg/kg/day for

27 days. The loading dose of 200 µg/kg in all cohorts is within the approved dose range of the summary of product characteristics[19] with the first cohort then having continuous daily dosing of 50 µg/kg/day for 27 days, the equivalent of a 200 µg/kg loading dose plus cumulative continuous daily dose of 1350 µg/kg (which is less than the CDC crusted scabies dose over a month, 1400 µg/kg) and combined dose would be less than 2000 µg/kg taken in split doses over one week.

The study has been designed to ensure the safety of the subjects by careful monitoring of individual subjects and review of safety data before dose escalation. The study design has the following features:

- Sentinel dosing for each cohort
- Safety data review before dose escalation
- Careful monitoring of the subjects with a one-week inpatient stay followed by once weekly on-site visits during the dosing phase and a final visit 2 weeks after the last dose.

In conclusion, for the proposed dosing regimen over 28-day period consisting of a first loading dose of 200 µg/kg followed by once daily dosing of either 50, 75 or 100 µg/kg/day for 27 days, in healthy volunteers, is expected to be well tolerated due to:

- Substantial exposure to Ivermectin since 1987
- Shorter duration of the study (4 weeks in humans vs 13 weeks in rats/dogs)
- Known safety profile of ivermectin at doses much higher than the approved dosages (up to 2000 µg/kg was tested in healthy volunteers with no significant increase in adverse events recorded compared to placebo) and the one-month treatment regimen for crusted scabies
- Study design, allowing for close monitoring of subjects and careful dose escalations after SRC reviews.

3.2.1. Safety Review Committee

Decisions for dose escalation between dose cohorts will be taken during an SRC meeting. The objectives of the SRC meetings are to review data from the current and previous cohort(s) and define the dose to be tested in the next cohort.

The SRC will comprise at a minimum:

- The Principal Investigator
- The Sponsor Medical Monitor
- MAC Project Manager for purpose of recording meeting minutes

Safety Review Committee meetings will be scheduled to occur once quality-controlled safety, tolerability and plasma PK data up to at least Day 14 are available from a minimum of 4 active and 1 placebo subjects. For the Cohort 2 data SRC meeting onwards, available safety, tolerability and plasma PK data up to Day 28 from previous cohorts will be reviewed.

The safety and tolerability data to be reviewed will include, at a minimum, AEs, physical examinations, comprehensive neurological examinations, 12-lead ECGs, vital signs and clinical laboratory evaluation results, summarised by the Investigator in an Interim Safety Report.

Further details on the operation of the SRC will be defined in a standalone supporting document. Details regarding the safety stopping criteria are provided in Section 3.2.2.

3.2.2. Dose Escalation and Adjustment Criteria

3.2.2.1. Criteria for Stopping Dose Escalation

- PK Stopping Criteria: based on review of the accumulation ratio (RA). Dose escalation will not proceed if this is deemed to pose a clinically significant risk to subjects by the SRC members.
- Safety Stopping Criteria: Dose escalation will not proceed if any of the following occur in ivermectin-treated subjects:
    - One or more Hy's Law cases in subjects who have been administered ivermectin. Hy's Law is defined as AST or ALT ≥3 x upper limit of normal (ULN) and bilirubin ≥2 x ULN, in the absence of a significant increase in alkaline phosphatase (ALP) and in the absence of an alternative diagnosis that could explain the increase in bilirubin.
    - A 'serious' adverse reaction (see Section 7.6.1.2 for definition of 'serious) in 1 subject, i.e., a serious adverse event (SAE) that is considered at least possibly related to ivermectin administration.
    - 'Severe' non-serious adverse reaction, i.e., a severe non-serious AE considered as at least possibly related to ivermectin administration, in 2 subjects in the same cohort, independent of within, or not within, the same system-organ class (SOC).
    - Clinically significant abnormalities in laboratory parameters in 2 or more subjects within the same cohort indicating dose-related intolerance, considered related to ivermectin.
    - Other findings that indicate dose escalation should be halted, e.g., if there is an unacceptable tolerability profile based on the nature, frequency and intensity of observed AEs and/or clinical safety monitoring.

If any of these stopping criteria are met, the SRC should stop further dose escalation. The SRC will determine whether the dose level should be repeated, whether a lower dose should be tested, or whether the study should be terminated. Progression to subsequent cohorts (which may include lower doses) may be approved by the SRC subject to satisfactory review of the available PK, safety and tolerability data. Alternatively, the SRC may conclude it is inappropriate to continue to another cohort, in which case the study will be terminated. If significant safety concerns arise during dosing of a cohort, the SRC will review all available data and, considering the criteria above, decide whether it is appropriate to continue.

3.2.2.2. Individual Stopping Criteria

- Any subject who experiences any of the criteria listed in Section 3.2.2.1.
- Investigator discretion based on clinical safety grounds.

4. STUDY SETTING

A single clinical research facility will be selected for this study.

5. STUDY TREATMENTS

5.1. Name and Description of Investigational Products

Ivermectin will be provided as 3 mg tablets [redacted]

Matching placebo will be manufactured by [redacted] and supplied with a certificate of analysis.

Further supportive information will be provided in the Pharmacy Manual.

The IMP supplied by the Sponsor is to be used exclusively in the clinical study according to the instructions in this Protocol and the Pharmacy Manual. Until the IMP is dispensed to the subjects, it should be stored at a controlled room temperature below 25°C. At home, subjects IMP will be stored at room temperature and kept out of the reach and sight of children.

The Principal Investigator will be responsible for storage and accountability of the IMP. Safety information regarding the IMP is provided in the IB.

5.2. Dose Administration

The active IMP or matched placebo will be orally administered in the morning from Day 1 to Day 28 following an overnight fast. Each dose will be taken with 240 mL of water at room temperature. Water will be allowed ad libitum and breakfast can be eaten between 1 to 2 hours after dosing. Dosing will be observed by CRU staff whilst resident in the CRU.

Body weight at Screening will be used to calculate the dose administered. For each dose level administered, the number of 3 mg tablets shown in Table 4 will be administered.

Table 4: Number of Ivermectin Tablets Per Cohort by Body Weight

	Loading Dose (Day 1)	50 µg/kg Daily Dose (Cohort 1; Day 2 to Day 28)	75 µg/kg Daily Dose (Cohort 2; Day 2 to Day 28)	100 µg/kg Daily Dose (Cohort 3; Day 2 to Day 28)
50 to ≤65 kg	4 tablets	1 tablet	1.5 tablets (first day 1 tablet, the next day 2 tablets, etc.)	2 tablets
≥66 to ≤79 kg	5 tablets	1 tablet	1.5 tablets (first day 1 tablet, the next day 2 tablets, etc.)	2.5 tablets (first day 2 tablets, the next day 3 tablets, etc.)
≥80 to ≤95 kg	6 tablets	2 tablets	2.5 tablets (first day 2 tablets, the next day 3 tablets, etc.)	3 tablets
≥96 to ≤110 kg	7 tablets	2 tablets	2.5 tablets (first day 2 tablets, the next day 3 tablets, etc.)	3.5 tablets (first day 3 tablets, the next day 4 tablets, etc.)

Non-whole weight values will be rounded to the nearest whole number. For example, 95.1 to 95.4 kg would be rounded down to 95 kg and 95.5 to 95.9 kg would be rounded up to 96 kg.

Before leaving the CRU on Day 7, subjects will be provided with a paper diary to record their daily dose of ivermectin or placebo (number of tablets taken, what time they took their dose and what time they had breakfast). Whilst outside the CRU, subjects will be contacted regularly by phone or text message to ensure that they are taking the correct number of tablets and to ensure that they are taking their dose following an overnight fast.

If a subject forgets to take their daily dose of ivermectin or placebo in the morning and has already eaten, they should not take their dose for that day.

The number of tablets to be taken can vary day-to-day. If a subject misses their daily dose of ivermectin or placebo then, on the following day, they should take the number of tablets they missed the day previously (e.g., if they are alternating between 1 tablet and 2 tablets per day and they missed 2 tablets, they should take 2 tablets the following day and 1 tablet the day after).

For the Day 14, Day 21 and Day 28 doses, subjects will NOT take their daily dose of ivermectin or placebo. Instead they will bring their remaining tablets to the clinic and will take their daily dose (overnight fasted) after any applicable pre-dose assessments have been performed by CRU staff. Dosing will be observed by CRU staff on all study visit days.

5.3. Concomitant Medication

The Investigator and study team may review medication use on a case-by-case basis to determine if its use would compromise subject safety or interfere with study procedures or data interpretation (exclusion criteria relating to concomitant medication are presented in Section 6.2). By exception, the subject may take paracetamol (less or equal 2 g/day) for up to 48 hours prior to first dosing. All concomitant medications used (including over-the-counter [OTC] medications and herbal supplements) will be recorded in the source documents and on the appropriate electronic case report form (eCRF).

5.4. Assessment of Compliance with Treatment

All doses will be administered by study staff under direct observation whilst resident in the CRU. The administration of the study drug will be recorded within the appropriate pages of the eCRF. Subjects will be asked to return all unused medication including empty and partially used containers. For the time when subjects administer at home (Day 8 to Day 27), study medication dispensed at the previous visit will be retrieved by the Investigator and compliance assessed by regular contact with the subject whilst outside the CRU, returned medication count and subject diary completion.

Any deviations from the planned dosing procedure will be recorded within the eCRF.

5.5. Blinding

This study will be double-blinded (Investigator- and subject-blinded). The randomisation list will be kept in a secure location until the end of the study. Only the Pharmacy staff involved in handling the study drug and laboratory staff responsible for analysing the PK blood samples will be unblinded during the study and will have access to the randomisation list.

5.6. Emergency Unblinding

The study blind should not be broken except in a medical emergency where knowledge of the IMP would inform treatment of an emergency. The Investigator has the sole responsibility for determining if unblinding of treatment is necessary for medical management of an event. The Investigator will inform the Medical Monitor and Sponsor of this decision as soon as is reasonably practicable. The applicable Standard Operating Procedures (SOPs) will be followed to break the blind.

After database lock, the overall randomisation code will be broken only for reporting purposes.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

The study population includes 24 healthy male subjects. Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

6.1. Inclusion Criteria

Subjects meeting the following criteria will be included in the study:

1. Subject is male, of any ethnic origin.
2. Subject is aged between 18 to 45 years, inclusive.
3. Subject has a body mass index (BMI) of 18.5 to 32.0 kg/m^2, inclusive.
4. Subject is ≥50 kg.
5. Negative RT-PCR Test for SARS-CoV-2 at Screening and negative lateral flow immunoassay test for SARS-CoV-2 at Day -1.
6. Willing and able to comply with scheduled visits, treatment plan, and other study procedures
7. Healthy as determined by a responsible physician, based on medical evaluation including medical history, physical examinations, neurological examinations, concomitant medication, vital signs, 12-lead ECG and clinical laboratory evaluations.
8. Male subjects must use a condom during the study and for 3 months after their final dose of study medication, if their partner is a woman of childbearing potential. In addition, their female partner of childbearing potential must use an additional method of highly effective contraception (see Section 6.3.1) from first dosing until 3 months following final dosing.
9. Provision of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

6.2. Exclusion Criteria

Subjects with any of the following will be excluded from study participation:

1. Clinically relevant history of abnormal physical or mental health (defined as any subject requiring medical, psychological or pharmacotherapeutic intervention for mental illness) interfering with the study as determined by medical history and physical examinations obtained during Screening and Day -1 as judged by the Investigator (including [but not limited to], neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder).
2. Clinically relevant abnormal laboratory results (including hepatic and renal panels, complete blood count, chemistry panel and urinalysis), 12-lead ECG and vital signs, or physical findings at Screening and/or Day -1 (as judged by the Investigator). In case of uncertain or questionable results, tests performed during Screening may be repeated once to confirm eligibility or judged to be clinically irrelevant for healthy subjects.

3. Refractory nausea, vomiting, or chronic gastrointestinal disorders, inability to swallow the study drug or having undergone extensive bowel resection which may affect adequate absorption of ivermectin
4. Any other concomitant disease or condition that could interfere with, or for which the treatment might interfere with, the conduct of the study as outlined in this Protocol, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
5. Subjects with Gilbert's syndrome or AST, ALT, gamma-glutamyl transferase (GGT) or total bilirubin levels greater than the ULN at Screening or Day -1. These laboratory evaluations may be repeated once at the discretion of the Investigator. If the repeat test is within the reference range, the subject may be included only if the Investigator considers that the previous finding will not introduce additional risk factors and will not interfere with interpretation of safety data.
6. Known hypersensitivity or allergy to any component of the ivermectin drug product or placebo.
7. Evidence of previous SARS-CoV-2 infection from medical history.
8. Ophthalmologic disorder (moderate and severe retina or optic nerve pathology; cataracts excluded).
9. Subjects with a diagnosis of asthma or any other respiratory condition.
10. A neurologic disorder that may compromise blood brain barrier permeability (stroke within 90 days, brain tumour, multiple sclerosis, or other neuroinflammatory condition, a neurodegenerative disorder, epilepsy) or history of seizures.
11. QTcF >450 msec at Screening or at check-in on Day -1, following triplicate ECG readings.
12. Positive test for hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (anti-HCV) or human immunodeficiency virus I and II (anti-HIV I/II) at Screening.
13. Positive urine test for drugs of abuse, urine cotinine test or alcohol breath test at Screening or Day -1.
14. History of drug and/or alcohol abuse within the last 2 years, or intake of >21 units of alcohol weekly, and the inability to refrain from alcohol use from 48 hours before Screening and from 48 hours before Day -1 until the end of the study. One unit is equivalent to a 285 mL glass of full-strength beer or 1 (30 mL) measure of spirits or 1 glass (100 mL) of wine.
15. Use of tobacco and/or nicotine containing products (including e-cigarettes) within 3 months of Screening.
16. Habitual and heavy consumption of caffeinated beverages (>8 cups of coffee or equivalent per day) at Screening; and/or unable to refrain from use of (methyl) xanthine (e.g., coffee, tea, cola, chocolate) from 48 hours prior to each clinic visit until the end of the study.

17. The subject has participated in a clinical study and has received a medication or a new chemical entity within 3 months or 5 half-lives (whichever is longer) prior to first dosing of current study medication.

18. Use of any prescription or non-prescription medications, including herbal and nutritional supplements, or OTC medications (e.g., ibuprofen, aspirin) within 14 days of first dosing and throughout the study. By exception, the subject may take paracetamol (less or equal 2 g/day) for up to 48 hours prior to first dosing. The Investigator and study team may review medication on a case-by-case basis to determine if its use would compromise subject safety or interfere with study procedures or data interpretation.

19. Use of any drugs that are known substrates of CYP3A4, P-glycoprotein (P-gp) from within 4 weeks of Screening and unable to refrain from them until the end of the study (e.g., rifampicin, quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, indinavir, ritonavir or cobicistat). Use of critical CYP3A4 substrate drugs such as warfarin or coumarin anticoagulants.

20. Recent or expected microfilaricidal drug use, including ivermectin, or travel history to areas that are endemic for Loa loa or onchocerciasis (Angola, Cameroon, Central African Republic, Chad, Democratic Republic of Congo, Ethiopia, Equatorial, Guinea, Gabon, Republic of Congo, Nigeria and Sudan).

21. Use of medications having potential activity against SARS-CoV-2 such as hydroxychloroquine, chloroquine, lopinavir, ritonavir, remdesivir, azithromycin, in the 30 days prior to Screening and unable to refrain from them until the end of the study.

22. History of severe adverse reactions or allergies, or history of an anaphylactic reaction to prescription or non-prescription medication or food (non-active hay-fever is acceptable).

23. Consumption of any food or drinks containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits) within 14 days prior to first dosing until the end of the study.

24. Strenuous exercise within 48 hours prior to each blood collection for clinical laboratory tests.

25. Donation of blood or plasma of >400 mL within 4 weeks prior to first dosing until 4 weeks after final dosing.

26. Male subject who will not abstain from sperm donation between first dosing and 3 months after final dosing.

6.3. Study Restrictions

6.3.1. Contraception Restrictions

Male subjects with a female sexual partner of child-bearing potential must wear a condom (from first dosing until 3 months after final dosing) in addition to their female partner using a highly effective method of contraception, from first dosing until 3 months following final dosing. Contraceptive methods that can achieve a failure rate of less than 1% per year when

used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Surgical sterilisation

If the male subject is vasectomised then this will be accepted as a second form of highly effective contraception, in addition to the subject also wearing a condom. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with study treatment and must be part of the preferred and usual lifestyle of the subject.

6.3.2. Lifestyle Restrictions

Subjects should abstain from strenuous exercise for 48 hours prior to each visit for blood collection for clinical laboratory tests, and while in the CRU. Subjects should not start any new exercise regimes during their participation in the study.

6.3.3. Meals and Dietary Restrictions

The subjects are required to adhere to the following restrictions:

- Subjects should refrain from consumption of any food or drinks containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits) within 14 days prior to first dosing until the end of the study.
- Subjects should abstain from alcohol for 48 hours prior to Screening and no alcohol should be consumed from 48 hours prior to Day -1 until the end of the study.
- Subjects should abstain from tobacco and nicotine-containing products for 3 months prior to Screening, throughout the study until completion of the study.
- Subjects should abstain from (methyl) xanthine- and caffeine-containing products for 48 hours prior to each clinic visit until the end of the study.

- Subjects will be fasted overnight before dosing. Water will be allowed ad libitum and breakfast can be eaten between 1 to 2 hours after dosing. Standard meals and drinks will be provided while resident in the CRU. In addition, subjects should fast at least 4 hours prior to any visit where clinical laboratory evaluations will be carried out.
- Subjects should refrain from consuming poppy seeds 48 hours prior to Screening, Day -1, Day 14, Day 21 and Day 28 to avoid a positive result on the drugs of abuse screen.

6.4. Subject Withdrawal Criteria

For all subjects withdrawn from the study, discontinuation procedures as described in Appendix 1 should be conducted prior to discharge in the study. Subjects will be replaced if there are insufficient evaluable subjects in each dose cohort. A minimum of 4 ivermectin and 1 placebo subjects in each cohort are required for dose escalation and a minimum of 5 ivermectin and 1 placebo subjects are required for completion of a dose cohort.

Reserve subjects will be screened and admitted to the CRU on Day -1. They will undergo the Day -1 and pre-dose assessments but will not be dosed on Day 1, unless replacing another subject who fails inclusion/exclusion criteria.

Reasons for withdrawal or discontinuation at any time during the study may include any of the following reasons:

- Adverse event: Clinical or para-clinical events occurred that, in the medical judgement of the Investigator for the best interest of the subjects, are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to the study medication.
- Withdrawal of consent: The subject desired to withdraw from further participation in the study in the absence of an Investigator determined medical need to withdraw. If the subject gave a reason for withdrawing it should be recorded in the eCRF.
- Investigator decision.
- Compliance: any subject who fails to take their daily dose for 2 consecutive days, misses 3 doses in a week (7 days), or misses greater than 1 dose of study drug per week (>4 in total during 4-week study).
- Lost to follow-up: The subject stopped coming for visits and study personnel were unable to contact the subject.
- Other: The subject was discontinued for a reason other than those listed above, such as termination of the study by the Sponsor. The reason(s) should be recorded in the eCRF.

6.5. Follow-up Procedures

The Investigator will make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to attend the follow-up visit. All discontinuations and the reason for early discontinuation will be documented by the Investigator, and if appropriate on the AE form.

7. SAFETY ASSESSMENTS

Baseline safety data assessments for all parts of the study will be collected pre-dose at the nearest timepoint to dosing as shown in Appendix 1. The subjects will attend a Follow-up visit 14 days after the final dose for safety follow-up procedures [redacted]

7.1. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed including clinical chemistry, haematology, coagulation and urinalysis as indicated in the table below (Table 5). Serology, drugs of abuse, cotinine and alcohol screen will be performed as indicated in the table below (Table 5). [redacted]

All blood and urine analyses will be conducted at the sampling times [redacted]. The clinical laboratory evaluation results will be collected at Day -1, in time for results to be reviewed prior to dose administration. For abnormal values, additional testing may be performed, or clinical laboratory evaluations may be added to evaluate the abnormal values. Clinically significant values should be followed until resolution or until they reach a stable state.

Table 5: Clinical Laboratory Evaluations

Blood Chemistry BUN Creatinine Glucose Sodium Potassium Phosphate Chloride Calcium AST ALT GGT Alkaline phosphatase Total bilirubin Uric acid Albumin Total protein Lactate dehydrogenase	**Urinalysis (dipstick)** Glucose Bilirubin Ketone Specific Gravity Blood pH Protein Urobilinogen Nitrite Leukocyte Esterase Microscopic analysis if dipstick is abnormal
Haematology Haemoglobin Haematocrit RBC count RBC indices (MCV, MCH, MCHC) Platelet count White blood cell count with differential	**Drugs of abuse** Amphetamines Barbiturates Benzodiazepines Cocaine Cannabinoids Opiates
Coagulation Prothrombin time International normalization ratio Activated partial thromboplastin time	**Serology** Anti-HIV I/II SARS-CoV-2 (performed only if lateral flow immunoassay testing is positive) Anti-HCV HBsAg
Other Screens Alcohol (breath) Cotinine (urine) SARS-CoV-2 RT-PCR test	

Abbreviations: ALT – alanine aminotransferase; Anti-HIV I/II – Anti-human immunodeficiency virus I and II; Anti-HCV – anti-hepatitis C antibody; AST: aspartate aminotransferase; BUN – blood urea nitrogen; GGT – gamma-glutamyl transferase; HBsAG – hepatitis B surface antigen; MCV – mean corpuscular volume; MCH - mean corpuscular haemoglobin; MCHC – mean corpuscular haemoglobin concentration; RT-PCR – reverse transcription polymerase chain reaction.

7.2. 12-lead Electrocardiogram

A 12-lead ECG will be collected at the timepoints indicated in the Schedule of Assessments [redacted] The 12-lead ECG will be collected in triplicate, approximately 1 minute apart, at Screening, Day -1 and within 2 hours pre-dose on Day 1. Single readings will be collected at all other timepoints. 12-lead ECGs should be obtained after the subject has rested in the supine position for at least 5 minutes. In the event of an abnormal finding, recordings should be performed in triplicate. The ECG machine used should automatically calculate the heart rate and PR, RR, QRS, QT and QTcF intervals.

For timepoints with multiple assessments:

- collect the ECG first,
- then vital signs,
- then the PK blood draw. The PK sample should be collected at the scheduled time post-dose.

7.3. Vital Signs and Oral Temperature

Supine and standing vital signs (2 minutes apart), including heart rate, blood pressure and oral temperature will be collected at the timepoints in the Schedule of Assessments [redacted] Pre-dose vital signs should be collected within 30 minutes pre-dose.

For timepoints with multiple assessments:

- collect the ECG first,
- then vital signs,
- then the PK blood draw. The PK sample should be collected at the scheduled time post-dose.

7.4. Physical Examinations

A full physical examination, including height, BMI, and body weight, and assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular system, abdomen (liver and spleen), lymph nodes and extremities will be conducted at the times indicated in the Schedule of Assessments [redacted] A symptom-guided physical examination will also be conducted at the times indicated in the Schedule of Assessments [redacted]

7.5. Neurological Examinations

A comprehensive neurological examination will be conducted at the times specified in the Schedule of Assessments [redacted] The comprehensive neurological examination will include assessment of mental status and cognitive function, cranial nerve examination, motor function, sensation and proprioception (light touch, vibration), deep tendon reflexes of all 4 limbs, balance, co-ordination, gait and visual assessments. Visual assessments will include

visual inspection of the eyes, pupil response, eye movements, fundoscopy, visual acuity (Snellen chart) and visual fields.

7.6. Adverse Event Reporting

Adverse event monitoring will be conducted at the times specified in the Schedule of Assessments [redacted] Adverse events will be elicited through non-leading questions and spontaneous reporting by subjects. The Investigator is responsible for evaluating AEs and for the appropriate medical care of subjects during the study.

7.6.1. Definition and Criteria

7.6.1.1. Adverse Event

An AE is any untoward medical occurrence in a study subject which either emerges, or worsens from Screening, during the clinical study, regardless of its potential relationship to the medicinal product. An AE, therefore, can be any unfavourable or unintended sign, including a clinically significant abnormal laboratory finding, symptom, or disease temporally, whether or not it is considered to be study medication related.

Examples of an AE include:

- Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed.
- Signs or symptoms of a drug interaction.
- Signs or symptoms of a suspected overdose of either IMP or a concurrent medication (overdose per se should not be reported as an AE/SAE)
- A new laboratory abnormality occurring after the start of the study (i.e., after Screening) that results in subject withdrawal from the study or medical treatment or further follow-up.
    - Note: abnormal laboratory or other values obtained during Screening that preclude a subject from entering the study are not considered AEs but will be recorded.

Adverse events may include pre- or post-treatment events that occur as a result of Protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

A medical intervention to address an AE is an "action taken" and not an AE itself.

7.6.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death,
- Is life-threatening,
    - Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer

to an event, which hypothetically might have caused death, if it were more severe.

- Requires hospitalisation or prolongation of existing hospitalisation,
    - Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out setting. Complications that occur during hospitalisation are AEs. If complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.
- Results in persistent or significant disability or incapacity,
    - Note: The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital abnormality or birth defect,
- Is an important medical event.
    - Note: Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening, or result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.
    - Note: The terms "serious" and "severe" ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is NOT the same as "serious", which is based on subject/event outcome or action criteria described above and are usually associated with events that pose a threat to a subject's life or functioning. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.6.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry and haematology) or other abnormal assessments (e.g., ECGs, vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. Liver chemistry thresholds have been designed to assure subject safety. When subjects meet the hepatic transaminase threshold criteria (AST or ALT ≥3 x ULN), the subject should undergo close observation, including monitoring for symptoms (clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash) and hepatic function (AST, ALT, ALP), and fractionated bilirubin at least every 48 hours, until symptoms and/or hepatic function abnormalities resolve, stabilise, or return to baseline values. This event should be reported to MedinCell within 24 hours of learning of its occurrence. Appendix 4 represents the decision tree for whether or not study medication will be discontinued. A specialist or hepatology consultation should be considered in cases of protocol-mandated study medication discontinuation.

In addition, every attempt should be made to obtain the following for any subject who meets the hepatic transaminase threshold criteria:

- Viral hepatitis including: hepatitis A immunoglobulin (IgM) antibody, hepatitis B surface antigen and hepatitis B core antibody (IgM), HCV RNA, cytomegalovirus IgM antibody, Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophil antibody or monospot testing), and hepatitis E antibody (if subject resides outside UK or has travelled outside UK in past 3 months).
- Serum creatine phosphokinase and lactate dehydrogenase. Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form.
- Record use of concomitant medications, including paracetamol, herbal remedies, other OTC medications, putative hepatotoxins, or alcohol on the concomitant medications report form.
- The following are required for subjects with AST or ALT ≥3 x ULN and bilirubin ≥2 x ULN, but are optional for other abnormal liver chemistries:
    - Anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies.
    - Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease.

7.6.1.4. Pharmacokinetic Sampling Associated with Serious Adverse Events or Severe Adverse Events

Every possible attempt will be made to collect an unscheduled PK sample if a subject experiences an SAE or a severe AE. As the determination of an SAE or a severe AE is sometimes retrospective, unscheduled PK samples obtained when an event that is suspected to be serious or severe are also permitted.

7.6.2. Evaluating Adverse Events and Serious Adverse Events

All AEs will be assessed on 2 descriptive parameters: intensity (severity) and relationship to the study medication:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the study medication.

The intensity of each AE (including SAEs) will be recorded in the eCRF and assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

For AEs and SAEs, the relationship to the study treatment is to be assessed according to the following definitions:

Not related: There is no reasonable association between the study treatment and the suspected event.

Unlikely related: It is doubtful that there is an association between the study treatment and the suspected event. The event could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Possibly related: The suspected AE may or may not follow a reasonable temporal sequence from study drug administration. The event could have been produced or mimicked by the subject's clinical state or by other modes of therapy concomitantly administered to the subject.

Probably related: The suspected AE follows a reasonable temporal sequence from study treatment administration, abates upon discontinuation of the treatment; and cannot be reasonably explained by the known characteristics of the subject's clinical state.

When assessing the relationship to the study medication, the following criteria will be considered:

- Known class effect
- Positive rechallenge

- Positive dechallenge (resolution upon stopping the suspect study medication, in absence of other interventional treatment]
- Biological plausibility
- Lack of alternative explanation – concomitant drug or disease

7.6.3. Reporting Procedures and Requirements

7.6.3.1. Adverse Events

Events meeting the criteria in Section 7.6.1.1 occurring from the time of signed informed consent will be considered as AEs. All AEs between Screening to the Follow-up visit will be recorded in source and eCRF, whether or not considered study medication related. All AEs that are possibly or probably related to study medication will be followed until resolution or database lock, whichever occurs first. Also, the sign, symptom, or disease present before the baseline AE assessment are only considered AEs if they worsen after this point. Any AEs already documented at a previous assessment and designated as ongoing should be reviewed at subsequent visits as necessary. If these have resolved, this should be documented. Changes in intensity or frequency of AEs should be recorded as separate events (i.e., a new record started). The Investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (e.g., "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Section 7.6.1.1.

7.6.3.2. Serious Adverse Events

Each AE will be assessed to determine whether it meets seriousness criteria (Section 7.6.1.2). If the AE is considered serious the Investigator should report this event to the Sponsor. The Sponsor will report the event to the research ethics committee (REC) according to its SOPs. Serious adverse events occurring from the time of signed informed consent to the follow-up visit or 7 days after the last dose of study medication (whichever occurs later) will be recorded in source and electronic data capture; ongoing SAEs after this time frame will be followed until the Investigator, Medical Monitor, and Sponsor agree that the SAE is satisfactorily resolved, or stably unresolved. Serious adverse events considered by the Investigator to be related to study medication, regardless of the time of onset after treatment, should be reported. All information about SAEs will be collected and reported via the SAE form and sent by email message (contact information will be contained in the Investigator site file). The Investigator should send the initial report within 24 hours of becoming aware of the SAE. At a minimum, the initial report should include the following information:

- Event
- Seriousness criteria
- Protocol number
- Subject number, initials and date of birth
- Study medication
- Reporter name and contact information

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilisation and for reported deaths, the Investigator should supply MedinCell or its designee and the REC with any additional requested information (e.g., autopsy reports and terminal medical reports), if available. The original SAE form should be kept at the study site. The Investigator will be responsible for determining and in turn, reporting SAEs to the Sponsor. MedinCell or its designee will be responsible for reporting SAEs to regulatory authorities according to the applicable regulatory requirements. MedinCell or its designee will be responsible for completing the safety report and for notifying the relevant authorities of any SAE as outlined in the International Council for Harmonisation (ICH) Guidelines and per local regulatory requirements.

7.6.4. Prompt Reporting of Serious Adverse Events

Any SAE, occurring in a subject receiving treatment or if the Investigator becomes aware of any SAE post-treatment during the follow-up visit, should be reported by the Investigator to the Medical Monitor within 24 hours even if the SAE does not appear to be medication-related. An emailed copy of the SAE form, in addition to other related information should be sent to the appropriate Pharmacovigilance Vendor (PV). Additionally, it may be necessary for the Medical Monitor or Sponsor to directly communicate with the Investigator if additional information is required.

All additional follow-up evaluations should be reported to MedinCell or its designee. Such data should be emailed to the PV within 10 calendar days. Serious adverse events occurring from the time of signed informed consent to the follow-up visit or 7 days after the last dose of study medication (whichever occurs later) will be recorded in source and electronic data capture; ongoing SAEs after this time frame will be followed until the Investigator, Medical Monitor, and Sponsor agree that the SAE is satisfactorily resolved, or stably unresolved. Serious adverse events considered by the Investigator to be related to study medication, regardless of the time of onset after treatment, should be reported.

MedinCell or its designee is responsible for the reporting of SUSARs. An AE will be considered unexpected if the nature, severity, frequency of the event is not consistent with the risk information previously described for the IMP. The process for recording and reporting SUSARs is defined in the Sponsor or its designee SOPs in accordance with regulatory guidelines.

A list of expected serious adverse reactions are provided in the IB.

7.6.5. Special Considerations

7.6.5.1. Pregnancy of Female Partner of Male Subject

If the female partner of a male subject becomes pregnant between dosing and 3 months after dosing, the Investigator should report pregnancy within 72 hours after learning of the pregnancy. The Investigator should contact the designated individual(s) following the SAE notification process and record information related to the pregnancy on the designated pregnancy form provided by MedinCell or its designee. Early discontinuation visit assessments are required as soon as possible after learning of the pregnancy. The Investigator is also responsible for following any pregnancy following admission until delivery or termination if possible. These findings should be reported on the pregnancy form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous

abortion, congenital anomaly or reports of suspected adverse reactions in the neonate that are classified as serious.

7.7. Other Assessments

Assessments to be performed at Screening only and Day -1 only are detailed in the Schedule of Assessments [redacted]

8. PHARMACOKINETIC ASSESSMENTS

8.1. Pharmacokinetic Sampling

Baseline PK blood samples will be collected within 15 minutes before first dosing.

Blood samples for determination of plasma concentrations of ivermectin will be taken at the timepoints stated in [redacted]

The actual times of collection will be recorded.

Plasma concentration-time data will be analysed by noncompartmental methods. Nominal times may be used for interim decisions, however actual sampling times will be used for final calculations.

8.2. Storage and Analysis of Clinical Samples

Approximate sampling volumes are provided in [redacted] Samples will be collected, labelled, stored and shipped as detailed in the Sample Handling Sheets.

Pharmacokinetic blood (collected in K_2EDTA tubes) samples will be collected and ivermectin will be quantified using a validated liquid chromatography-tandem mass spectrometry (LC/MS-MS) method. Further details will be provided in a standalone document.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11. STATISTICS AND DATA ANALYSIS

11.1. Randomisation and Subject Allocation

A randomisation scheme will be produced by MAC Clinical Research. After informed consent is obtained, subjects will be allocated a unique screening number.

Only subjects who comply with all the inclusion criteria, and none of the exclusion criteria will be randomised onto the study. The subjects will be assigned to a randomisation number in the order of recruitment. The randomisation number will have 4 digital numbers, with the first being the cohort (i.e., 1 for Cohort 1, 2 for Cohort 2, etc), the second being whether a subject is a replacement (0 = original; 1 = replacement), and the last 2 being the subject number; for example, 1001 means the 1st subject in the originally randomised Cohort 1, whereas 1101 is the replacement of 1001. All screened subjects should be identifiable throughout the study.

11.2. Sample Size Determination

It is planned to enrol 24 subjects. An appropriate sample size cannot be determined statistically as no previous human data are available for continuous daily dosing. A sample size of 8 subjects (6 active:2 placebo) per dose level of ivermectin, with 3 dose levels was selected to be able to characterise the PK profile and produce safety information which can be compared with the known safety profile of ivermectin.

11.3. Statistical Analysis Plan

A Statistical Analysis Plan (SAP) will be prepared after finalising the Protocol and before database lock. The specifications in this document will detail the implementation of all the planned statistical analyses in accordance with the principal features stated in the Protocol. The SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivation.

11.4. Analysis Sets

The following analysis sets are defined for this study.

11.4.1. Safety Set

The Safety Analysis Set will consist of all subjects who received at least 1 dose of study drug(s). Subjects in the Safety Analysis Set will be classified according to study drug(s) they actually received. Safety data will not be formally tested but will be summarised using descriptive statistics.

11.4.2. Pharmacokinetic Analysis Set

All subjects who receive at least 1 dose of IMP per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK Analysis Set. The population will be defined by the Study Physician, Pharmacokineticist and Statistician prior to any analyses being performed.

11.4.3. Per-protocol Analysis Set

The Per-protocol Set will include all randomised subjects that have completed the 28-day dosing period of the trial without major protocol deviations. Subjects withdrawn due to non-compliance (see Section 6.4) will not be included in the Per-protocol Set. Subjects will be classified according to study drug(s) they actually received.

11.5. Statistical Analysis

Statistical analyses will be performed using SAS 9.4.

11.5.1. Safety Statistical Analysis

Safety assessments will include standard laboratory safety evaluations (haematology, biochemistry, coagulation and urinalysis), vital signs (blood pressure, heart rate and oral temperature), physical examinations, neurological examinations, 12-lead ECG and AE monitoring.

11.5.1.1. Adverse Events

All AEs will be listed according to SOC and preferred term (PT) assigned to the event using Medical Dictionary for Regulatory Activities (MedDRA; highest version). Number and percentage of subjects who experienced any AEs will be summarised by cohort and treatment. Furthermore, AEs will be summarised by causality and the maximum intensity. Any SAEs and/or AEs that led to withdrawal will be listed.

11.5.1.2. Clinical Laboratory Evaluations

Clinical Laboratory evaluation results will be listed and compared to laboratory reference ranges, with those values outside of the applicable range flagged as high (H) or low (L). The quantitative laboratory data will be summarised using descriptive statistics (n, arithmetic mean, median, minimum and maximum) for each parameter by treatment, time and cohort. Urinalysis data will be listed only.

11.5.1.3. Vital Signs

Vital signs (supine and standing systolic blood pressure, diastolic blood pressure, heart rate and body temperature) will be listed for individual subjects. Summary statistics (n, arithmetic mean, median, minimum, and maximum) will be calculated for each parameter by treatment, time, and cohort.

11.5.1.4. 12-Lead Electrocardiogram

Standard 12-lead ECG parameters (RR, PR, QRS, QT, QTcB, QTcF intervals and heart rate) will be listed for individual subjects. Out-of-range ECG values will be flagged as high (H) or low (L). Summary statistics (n, arithmetic mean, median, minimum, and maximum) will be calculated for each parameter by treatment, time, and cohort. Where multiple values are recorded at a timepoint for a subject, the mean of the values will be used in the summary statistics.

11.5.1.5. Neurological Examination

Neurological examination parameters will be listed for individual subjects. Frequency tables will be calculated for each parameter (percentage normal/abnormal) by treatment, time, and cohort.

11.5.1.6. Physical Examination

Physical examination data will be listed only.

11.5.2. Pharmacokinetic Statistical Analysis

Ivermectin plasma concentrations and PK parameters will be summarised using all subjects in the Pharmacokinetic Set. Full details of the PK analysis will be included in the PK Analysis Plan.

11.5.2.1. Derivation of Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived from individual plasma concentration data of ivermectin by noncompartmental analysis. The PK parameters derived to assess the multiple dose PK of ivermectin are shown in Table 6.

Table 6: Pharmacokinetic Parameters

Abbreviation	Definition
C_{max}	Maximum plasma concentration
[redacted]	[redacted]
t_{max}	Time of maximum plasma concentration
AUC_{0-24h}	Area under the plasma concentration-time curve from zero to 24 hours
[redacted]	[redacted]
[redacted]	[redacted]
$t_{1/2}$	Apparent terminal half-life
RA	Accumulation ratio

11.5.2.2. Statistical Analysis of Pharmacokinetic Parameters

The ivermectin PK parameters AUC_{0-24h}, [redacted] $t_{1/2}$ will be generated using noncompartmental methods. C_{max} will be determined directly from the data. Steady state will be assessed from visual examination of the data. In addition, dose proportionality will be determined using a suitable statistical model.

[redacted]

[redacted]

11.6. Handling of Missing or Incomplete Data

Unrecorded values will be treated as missing. The appropriateness of the method(s) described for handling missing data will be reassessed and documented as the data review prior to database lock. Depending on the extent of the missing values, further investigation may be made into sensitivity of the analysis results to the method(s) specified.

12. DATA HANDLING AND RECORD KEEPING

12.1. Collection of Data

Data collected from each completed subject will be recorded on source documents, which will be entered into an eCRF. The Investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified against the source documents. If certain data are not available or not applicable this will be indicated as such within the appropriate area of the eCRF.

Screening failures (subjects who signed consent to take part in the study but were not dosed) will not be entered into the clinical study database.

Data produced by automatic devices with original printouts (i.e., clinical laboratory evaluation results, ECG traces) will be attached to the source documents. Clinical laboratory parameters will be provided in laboratory printouts which are to be signed by the Investigator. Comments on all clinically significant abnormal values will be provided and documented by the Investigator or appropriately recorded within the eCRF.

Adverse Events and Medical History will be reported by the MedDRA SOC and PT; the latest version will be applied to all terms. All Medical History and AEs will be included in the data listings. Furthermore, all Prior Medications and Concomitant Medications will be reported using the WHODRUG categorization; the latest version will be applied to all terms.

All Prior Medications and Concomitant Medications will be summarised within the data listings.

Any missing, implausible or inconsistent recordings within the eCRFs will be referred to the Investigator using data query validation procedures; will be documented and resolved for each individual subject before database lock is declared.

All processes pertaining to the Data Management activities will be detailed within the Data Management Plan.

12.2. Inspection of Records

Authorised representatives of MedinCell will be allowed to conduct site visits to the CRU for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability and subject records, study source documents and any other pertinent records relative to study conduct.

12.3. Retention of Records

The Investigator should maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the IMP for investigation. If it becomes necessary for MedinCell or a regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

13. MONITORING, AUDIT AND INSPECTION

13.1. Study Monitoring

During the study, a monitor from MedinCell or representative will have regular contacts with the CRU, for the following:

- Provide information and support to the Investigator.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the Protocol, that data are being accurately recorded in the eCRFs, and that IMP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any Protocol deviations not previously sent to MedinCell
- Confirm AEs and SAEs have been appropriately documented within eCRFs and confirm any SAEs have been communicated to MedinCell and those SAEs that met criteria for reporting have been provided to the REC.

The monitor will be available between visits if the Investigator or other staff needs information or advice.

13.2. Audits and Inspections

Authorised representatives of MedinCell, a regulatory authority, or the REC may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents. The inspection determines whether these activities were conducted, in addition to data being recorded, analysed, and accurately reported according to the Protocol; ICH-GCP and any applicable regulatory requirements. The Investigator is responsible for making contact with MedinCell immediately, if approached by a regulatory agency regarding an inspection.

13.3. Quality Control and Quality Assurance

To ensure compliance with GCP and all regulatory requirements, MedinCell, may conduct a Quality Assurance Audit.

13.4. Research Ethics Committee

The Investigator should obtain REC approval for the study. Initial REC approval, and all materials approved by the REC for this study including the subject consent form and recruitment materials, should be maintained by the Investigator and made available for inspection.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Ethical Conduct of the Study

The study will be conducted in accordance with the EU Clinical Trial Directive 2001/20/EC, the ICH guideline for GCP E6(R2) dated December 2016, and the ethical principles laid down in the Declaration of Helsinki. Current regulatory requirements will be followed, as applicable.

14.2. Ethics Review

The final study Protocol, including the final version of the Informed Consent Form (ICF), must be approved or given a favourable opinion in writing by a REC as appropriate. The Investigator should submit written approval to MedinCell before enrolling any subject into the study.

The Investigator is responsible for informing the REC of any amendment to the Protocol in accordance with local requirements. In addition, the REC must approve all advertising used to recruit subjects for the study. The Protocol must be reapproved by the REC upon receipt of substantial amendments, as local regulations require.

The Investigator is also responsible for providing the REC with reports of any reportable serious adverse drug reactions from any other study conducted with the IMP. MedinCell will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the REC according to local regulations and guidelines.

14.3. Written Informed Consent

Potential subjects will have a detailed verbal presentation of the nature, purpose, risks and requirements, in addition to receiving detailed written information provided in the Participant Information Sheet. They will have adequate opportunity to ask the physician presenting the study about any aspect of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. Once the subject is satisfied that they are willing to participate in the study, they will be asked to sign a copy of the study ICF. The subject's signed and dated informed consent must be obtained before conducting any study procedures. The Investigator must maintain the original, signed ICF. A copy of the signed ICF will be provided to the subject.

Data and samples collected up to the point of withdrawal can only be used after withdrawal if the subject has consented for this. Any intention to utilise such data should be outlined in the consent literature.

A subject may be rescreened for the study once, if:

- They were ineligible at the first screen due to a transient reason, such as an upper respiratory tract infection, which impacted the clinical laboratory results.
- They were eligible at first screen, but unable to take part in the study dates within the Screening window.
- The subject was finally not enrolled in the initial group, e.g., reserve subjects

In the case of rescreening, only the assessments that were performed more than 28 days before the new dosing date will be repeated. The CRU will maintain a record of all subjects screened

(i.e., who signed the ICF) and any subject who is rescreened will be allocated a new screening number. Records up to the time of premature termination should be completed. In the event that a subject does not receive a study treatment, the primary reason will be recorded. A list of the procedures conducted at Screening are presented in the Schedule of Assessments [redacted]

Informed consent will be obtained prior to the subject undergoing procedures that are specifically for the purposes of the study.

14.4. End-of-Study

The end-of-study is defined as completion of the clinical activities relating to the follow-up visit by the last subject.

14.5. Notification of Serious Breaches to Good Clinical Practice

A "serious breach" is a breach which is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the study; or,
- the scientific value of the study.

The Sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The Sponsor of a clinical study will notify the licensing authority in writing of any serious breach of:

- the conditions and principles of GCP in connection with that study; or
- the Protocol and/or any Protocol amendments relating to the study, within 7 days of an awareness of the breach.

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16. APPENDICES

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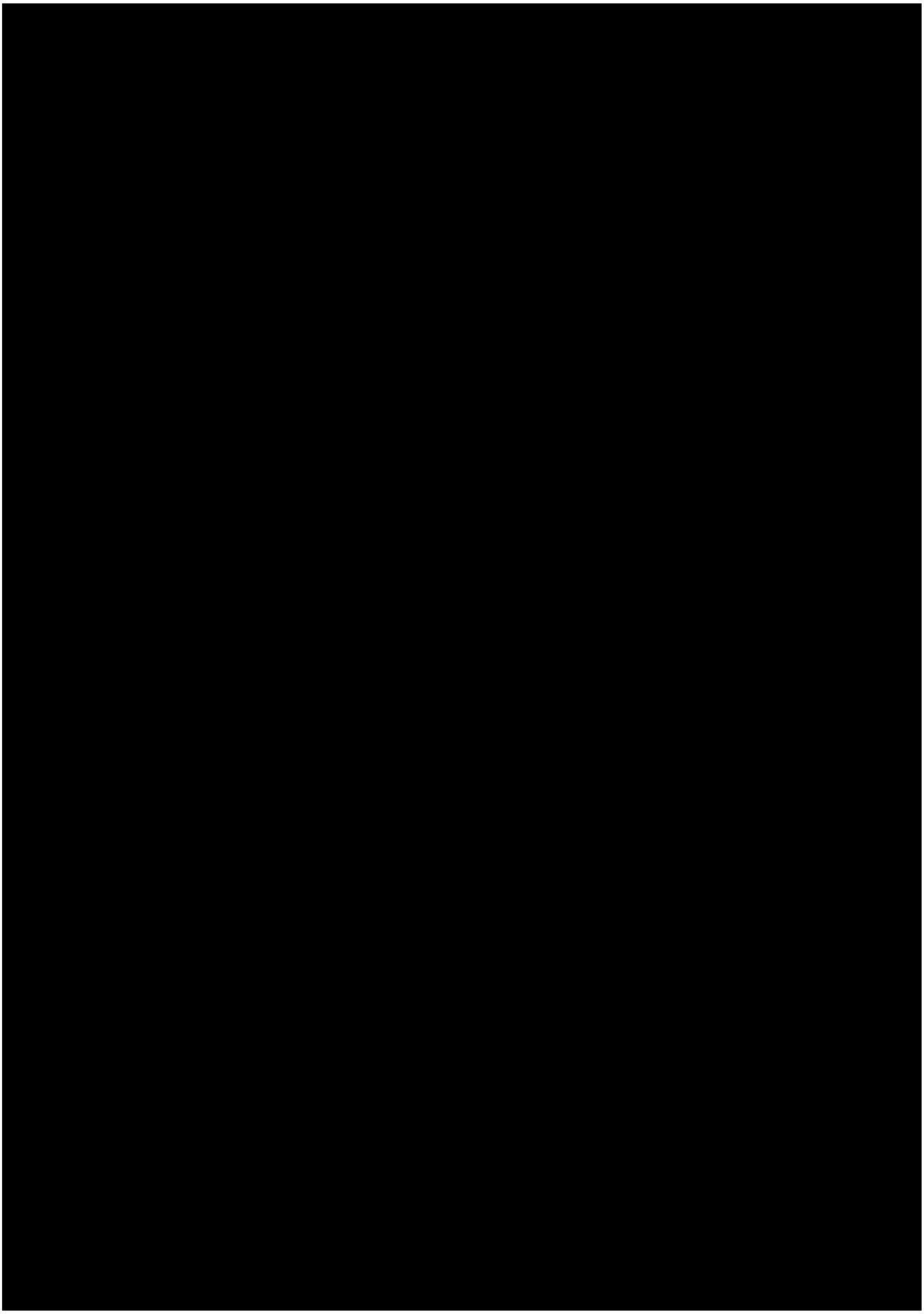
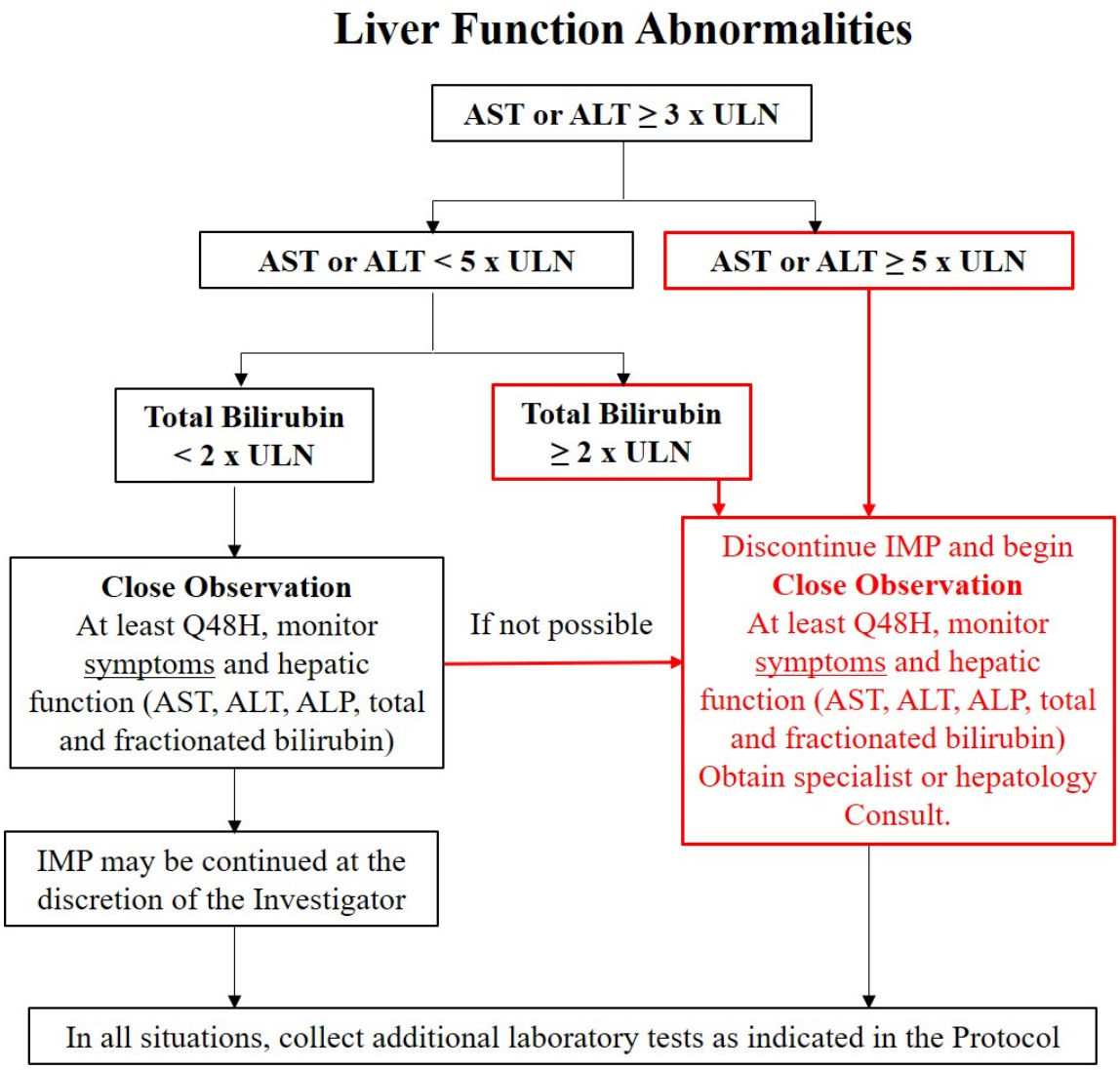


16.4. Appendix 4 – Liver Function Abnormalities Flowchart



Abbreviations: ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; IMP: investigational medicinal product; Q48H: every 48 hours; ULN: upper limit of normal.
* The following tests are required for subjects/patients with AST or ALT ≥3 x ULN and bilirubin ≥2 x ULN: Anti-nuclear antibody, anti-smooth muscle antibody, and type 1 anti-liver kidney microsomal antibodies, in addition to liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver diseases.