STATISTICAL ANALYSIS PLAN

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

STUDY CODE: [redacted]

MAC STUDY CODE: [redacted]

VERSION: 1.0
DATE: 08MAR21

Issued by:
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and special terms are used in this document.

Abbreviation	Explanation
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BP	Blood Pressure
BMI	Body Mass Index
eCRF	Electronic Case Report Form
CI	Confidence Intervals
Cmax	Maximum Concentration
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
GLMM	Generalised Linear Mixed Model
HR	Heart Rate
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
PRO	Patient reported outcome
PT	Preferred Term
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis system
SBP	Systolic Blood Pressure
SRC	Safety Review Committee
SOC	System Organ Class

Abbreviation	Explanation
SD	Standard Deviation
TFL	Tables, Figure and Listing
TEAEs	Treatment-Emergent Adverse Events
Tmax	Time taken to reach Cmax

1 STUDY DETAILS

1.1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to define the efficacy and safety analysis variables and analysis methodology to address the study objectives.

The pharmacokinetic (PK) analysis is outside the scope of this analysis plan. That analysis will be described in a separate document.

The Protocol dated 16 December 2020 (version 2.0) was used in the development of this statistical analysis plan.

1.2 STUDY OBJECTIVES

The objectives of the study are:

Primary Objective

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

Secondary Objective

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

Exploratory Objective

- The exploratory objective of this study is to evaluate the potential of ivermectin as a prophylactic measure to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection.

1.3 STUDY ENDPOINTS

1.3.1 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 ($t_{1/2}$).

1.3.2. Secondary Endpoint(s)

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.

1.3.3. 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.

1.4 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 postdose 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 1.

Table 1: 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 4.7).

[redacted]

[redacted]

2 ANALYSIS SETS

2.1 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 of study protocol) will not be included in the Per-Protocol Set. Subjects will be classified according to study drug(s) they actually received.

2.2 SAFETY ANALYSIS 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.

2.3 PHARMACOKINETIC ANALYSIS SET

All subjects who receive at least 1 dose of investigational medicinal product (IMP) per the Protocol for whom any postdose 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.

2.4 PROTOCOL DEVIATIONS

Protocol deviations will be categorised as minor/major and deviation category in a blinded manner prior to the database lock for each study part. The sponsor will review protocol deviations throughout the course of the study. All deviations will be listed.

3 DERIVED VARIABLES

3.1 EXPLORATORY ENDPOINT - OCCURRENCE OF SARS-COV-2 INFECTION

Occurrence of SARS-CoV-2 infection will be defined as either a positive PCR or positive serology test result at any point after first dose of the IMP.

4 ANALYSIS METHODS

4.1 GENERAL PRINCIPLES

All summary tables, figures and data listings will be produced using SAS software 9.4 or above.

Summaries will be performed by treatment group and overall.

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. For log-transformed data, the geometric mean, coefficient of variation (CV), median, minimum and maximum will be presented.

Categorical variables will be summarised by frequency counts and percentages for each category.

For AE summaries, the n and % of subjects with event, as well as the number of events, will be shown.

For all endpoints the last observation before the first dose of study treatment will be considered the baseline measurement unless otherwise specified. However, if an evaluable assessment is only available after randomisation but before the first dose of randomised treatment then this assessment will be used as baseline.

Assessments on the day of the first dose where neither time nor a nominal predose indicator are captured will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

In all summaries change from baseline variables will be calculated as the post-treatment value minus the value at baseline. The percentage change from baseline will be calculated as:

(post-baseline value - baseline value) / baseline value x 100.

All listings will be ordered by treatment group (ivermectin or placebo), cohort and subject number and will include all available data including unscheduled data.

Unscheduled values will be mapped to the closest prior nominal visit/timepoint. If multiple values exist for a nominal visit/timepoint then the worst value of available results will be used in the summary.

Listings will show the original visit and timepoint as collected on the electronic case report form (eCRF) as well as the mapped visit and timepoint for unscheduled values. An indicator will be included in the listings to indicate which value is utilised in the analysis.

4.2 SUBJECT ACCOUNTABILITY

Summaries of analysis populations and subject disposition will be summarised and listed using all subjects who have signed informed consent. The data summaries will contain the following information:

- Number of subjects randomised
- Number and percent of subjects who received ivermectin/placebo
- Number and percent of subjects who completed the study
- Number and percent of subjects who discontinued early from the study and reason for early discontinuation
- Number and percent of subjects in each of the analysis populations

4.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All randomized subjects will be used for all demographic and baseline characteristics summaries. All demographics and baseline characteristics data will be included in listings. The actual treatment (ivermectin / placebo) received will be utilised in these analyses.

4.3.1 Demographics

Demographics including age, ethnicity, height, weight, gender, body mass index (BMI) will be summarised appropriately. In general, for the continuous demographic variables (i.e., age, height, weight and BMI) results for each treatment group will be summarised using mean, standard deviation (SD), median, and minimum and maximum values. For categorical (nominal) variables (i.e., race, ethnicity, and gender), the number and percentage of subjects will be used.

4.3.2 Medical History

Medical history will be summarised by treatment group using number of observations and percentages of subjects reporting each category. Medical history will be coded into the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) available when coding activities commence.

4.3.3 Eligibility Laboratory Assessments

Pregnancy test, follicle stimulating hormone test, urine cotinine, urine drugs of abuse, alcohol breath screen, SARS-CoV-2 test and serology will be listed by subject, treatment, and timepoint, as appropriate.

4.4 PRIOR/CONCOMITANT MEDICATIONS AND RESCUE MEDICATIONS

All prior or concomitant and rescue medication data will be included in listings.

Medications will be reported using the most recent version of the World Health Organization drug (WHODRUG) codes available when coding activities commence. Medications will be classified according to the World Health Organization Drug Dictionary (WHODD Version March 2019 or later) ATC code levels 2 to 4.

Prior medications are defined as medications taken prior to the dosing of ivermectin/placebo.

Concomitant medications are defined as medications taken on or after the date/time of ivermectin/placebo regardless of the start date/time. Medications can be classified as both prior and concomitant. Prior and concomitant medications will also be listed by ATC code level 4. Actual treatment received will be utilised in summaries.

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[redacted]

[redacted]

4.6 SAFETY PARAMETERS

The objective of the evaluation of the safety variables is to investigate the data for any effects on clinical tolerability and laboratory safety variables.

Safety assessments include AE monitoring, standard laboratory safety evaluations (haematology, blood chemistry, coagulation and urinalysis), supine vital signs (RR, BP, HR and oral temperature), orthostatic vital signs, physical examinations, neurological examinations, and 12-lead ECG.

The analysis of safety will be descriptively summarised by timepoint, as appropriate. Data will be presented by actual treatment received for the purposes of summarising the safety results.

No formal hypothesis testing will be carried out.

4.6.1 Adverse Events

Adverse events will be listed in the following categories:

- Treatment-emergent adverse events (TEAEs) are any AEs with a start date and time on or after dosing with ivermectin/placebo. All TEAEs will be listed and summarised as indicated below

The overall incidence of TEAEs (number and percentage of subjects) as well as the number of events will be summarised by treatment, cohort and overall, categories of degree of severity, serious adverse events (SAEs), causally related TEAEs and SAEs, TEAEs leading to discontinuation of treatment and AEs or SAEs leading to withdrawal.

TEAEs will be summarised at both the subject [number (%) of subjects] and event [number of events] level for the following:

- System Organ Class (SOC) and PT
- SOC and PT and maximum reported severity
- SOC and PT and causal relationship to study drug

These analyses will be repeated for SAEs and treatment related AE if deemed necessary, otherwise only the SAEs by SOC and PT will be performed.

For the incidence at the subject level by SOC and PT; if a subject experiences more than one event within the same SOC and PT, only one occurrence will be included in the incidence.

[redacted]

[redacted]

For the incidence at the subject level by SOC, PT and severity; if a subject experiences more than one event within the same SOC and PT, only the most severe occurrence will be included in the incidence.

4.6.2 Clinical Laboratory Evaluations

Clinical laboratory evaluation results (chemistry, haematology, and coagulation) will be listed for individual subjects and compared to laboratory reference ranges and those values outside of the applicable range will be flagged as high (H) or low (L) and categorised by clinical significance (clinically significant/non-clinically significant). This classification of high, low and normal will be summarised by panel (i.e., chemistry, haematology, and coagulation), laboratory test, visit and timepoint.

For all laboratory variables, baseline value will be calculated as last laboratory value prior to dosing. Change from baseline values at each assessment will be calculated as the assessment value minus the baseline value. The quantitative laboratory data, along with changes from baseline will be summarised using descriptive statistics by timepoint, cohort and treatment.

Urinalysis data will be listed only.

4.6.3 Vital Signs

Vital signs data and oral temperature will be listed for individual subjects.

Vital signs include heart rate (HR), supine and standing systolic blood pressure (SBP), diastolic blood pressure (DBP), respiration rate and body temperature.

Vital signs data along with changes from baseline will be summarised using descriptive statistics by position and timepoint. For each vital sign variable, baseline value will be calculated from the mean of the available triplicate (if collected) predose values.

4.6.4 Electrocardiogram (ECG)

Standard 12-lead ECG parameters (PR, RR, QRS, QT, QTcF and HR) and ECG abnormal assessment will be listed for individual subjects.

For each ECG variable, baseline value will be calculated from the means of the available data prior to dose, if multiple values are recorded. Change from baseline values will be calculated as the assessment values minus baseline values.

Descriptive statistics will be calculated for absolute value of each parameter, together with the corresponding changes from baseline overall and by dose and timepoint. Where multiple values are recorded at a timepoint for a subject, the mean of the available values will be used in the summary statistics.

4.6.5 Physical examination

A summary table will be produced for each physical examination test reporting PI interpretation category (n and %) by cohort, timepoint and arm.

Physical examination data will be listed for individual subjects.

4.6.6 Neurological examination

A summary table will be produced for each neurological examination test reporting PI interpretation category (n and %) by cohort, timepoint and arm.

Neurological examination data will be listed for individual subjects.

4.7 SAFETY REVIEW COMMITTEE

SRC analysis is out of scope of this SAP and details are contained within the SRC charter.

5 HANDLING OF MISSING OR INCOMPLETE DATA

Unrecorded values will be treated as missing. Efforts will be made to prevent this from occurring. For complete missing visits the missing efficacy, safety will be treated as missing at random and will not be imputed in the statistical analysis except for partial dates.

For the exploratory efficacy analysis, frequency of missing data will be reported in a separate table as described within the analysis section.

5.1 PRIOR AND CONCOMITANT MEDICATION DATES

Partial dates for any prior and concomitant medications recorded in the eCRF will be imputed using the following convention:

- If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
- If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

The recorded partial date will be displayed in listings. No imputation will be performed for completely missing start and end dates.

5.2 AE START AND END DATES

The eCRF allows for the possibility of partial dates (i.e. only month and year) to be recorded for AE start and end dates; that is the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time of onset and the duration of the event:

- Missing Start Day: First of the month will be used unless this is before the start date of first study treatment; in this case the study treatment start date will be used and hence the event is considered treatment emergent.
- Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study completion; in this case the study stop date will be used.

Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

6 TABLE AND LISTING SHELLS

Tables, figures and listing (TFL) Shells will be provided as a separate document. The TFLs listed and the corresponding numbering may be subject to alteration. Tables and figures may be presented as in-text tables and figures in the CSR body.