Statistical Analysis Plan (SAP)

Sponsor:	MedinCell SA
Study Title:	A multicentre randomised, Double-Blind, Placebo-controlled **S**tudy to evaluate the effic**A**cy and safety of oral **IVE**rmectin tablets in the prevention of COVID-19 (the **SAIVE** Trial)
Protocol Version/Date:	2.0; 2021-12-20
SAP Version/Date:	1.0; 2022-07-20
Supersedes SAP Version:	NA
Appendices (external documents):	1. List of Tables, Listing, Figures (TLFs)

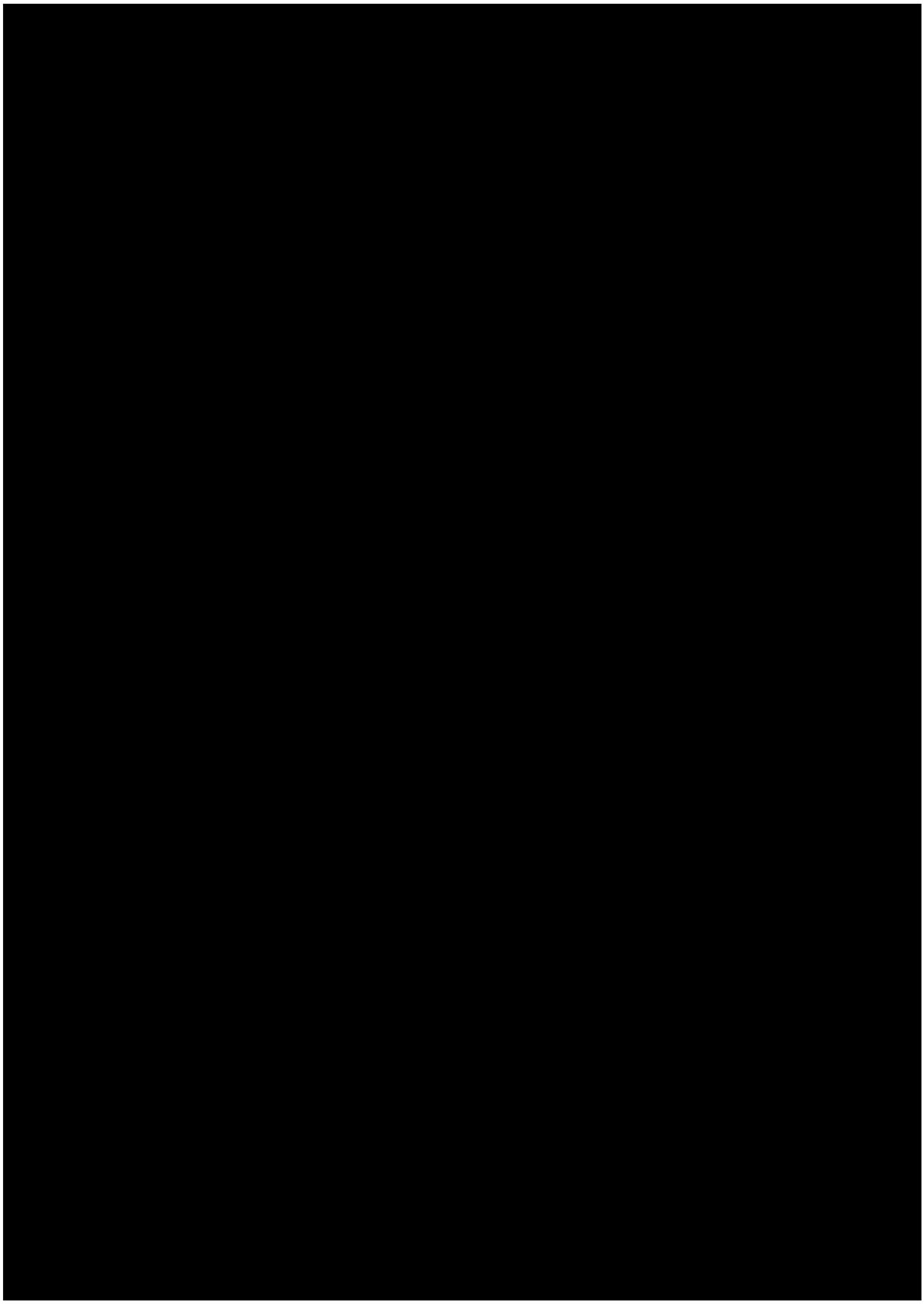
Approval

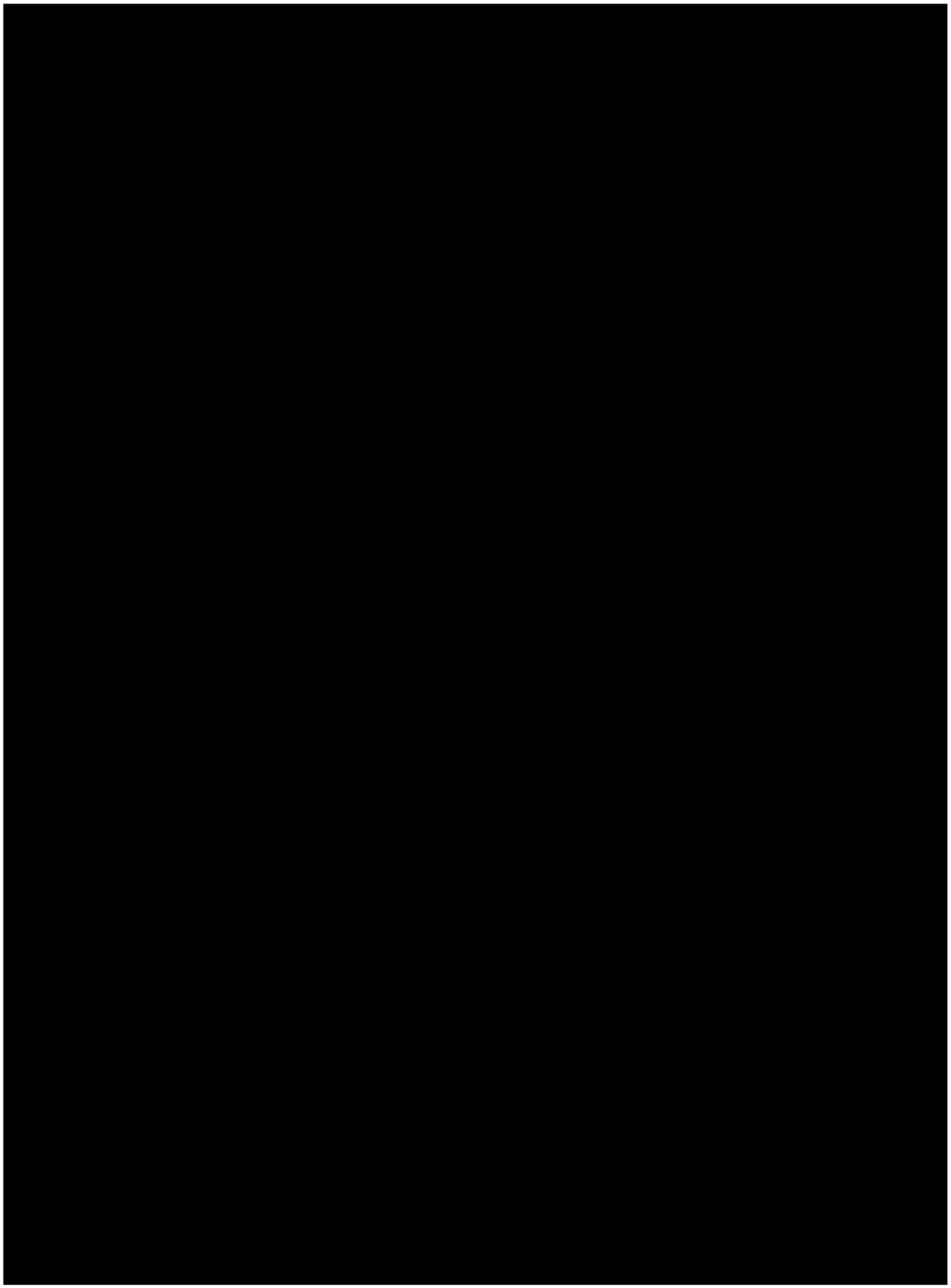
The Trial Statistician hereby confirms that the SAP was prepared in conformance with the procedures and principles set forth in the indicated protocol version and all established relevant guidelines.

Name **Affiliation, Function**	**Signature:**	**Date:**
[redacted]		

By signing hereafter, I confirm that this Statistical Analysis Plan adequately describes the statistical analyses to be performed in the context of this study.

Name **Affiliation, Function**	**Signature:**	**Date:**
[redacted]		





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1 STUDY INFORMATION

The aim of the present Proof of Concept Phase II clinical study is to:

- Demonstrate the efficacy of a continuous daily dosing for 28 days of ivermectin for the prevention of COVID-19 infection in humans,
- Consolidate current knowledge on the ivermectin safety profile,
- Collect data on potential ivermectin effects on COVID-19 clinical outcomes.

[redacted]

1.1 Primary objective

The primary objective of this study is to assess the efficacy of ivermectin compared to placebo in the prevention of laboratory-confirmed COVID-19 infection.

1.2 Secondary objectives

The following secondary objectives will be investigated:

- To assess the efficacy of ivermectin on Time to RT-PCR positive testing.
- To assess the efficacy of ivermectin on the occurrence of severe COVID-19 symptoms.
- To assess the efficacy of ivermectin on Time to first COVID-19 related clinical events.
- To assess the efficacy of ivermectin on the rate of COVID-19 related hospitalisations.
- To assess the efficacy of ivermectin on the rate of COVID-19 related mortality.
- To assess the safety and tolerability of ivermectin given for a period of 28 days.

1.3 Study design

This is a randomised, double blind, parallel-group, placebo-controlled, multicentric Phase II clinical trial evaluating the efficacy and safety of ivermectin tablets in the prevention of COVID-19 infection.

If all eligibility criteria are met, the participant will be randomised, and a loading treatment dose will be administered.

Participants will be assigned in a 1:1 ratio to receive oral daily treatment with either ivermectin or placebo. Randomisation will be performed stratified by country.

The study requires two visits to the study center, on Day 1 and Day 28, the first and last days of treatment. In addition, there will be 3 remote visits (day 4, day 7 and day 10) that can be conducted by telephone.

The treatment period lasts for 28 days in total, followed by a 28-day follow-up period, and there is a 2-day window period for visits. Therefore, total study duration for each participant is up to 58 days.

Ivermectin will be supplied as 3 mg tablets and will be administered orally, under fasting conditions, as follows: 200 ug/kg as the loading dose on Day 1 and then 100 ug/kg/day for

27 days. Control participants will receive placebo tablets, the number of tablets to be taken will match the number of IVM tablets taken by the active participants in the same body weight range.

1.4 Planned sample size

The sample size was calculated to compare the proportion of participants who become positive to SARS-CoV-2 RT-PCR within 1 month after randomisation between the two groups: Placebo group and ivermectin group. The assumptions are based on results of a study assessing the transmission of SARS-CoV-2 infections in households carried out in the US between April and September 2020. Thus it is expected that the proportion of participants becoming infected in the placebo group is 54% or higher (Grijalva et al, 2020). Furthermore, a reduction by 20% is expected in the ivermectin group (OR=2.28).

When requiring a power of 90% (1-β) and a significance level of 5% (α), then according to the Casagrande & Pike formula the required sample size to detect such difference with a test of comparison of two proportions is equal to 138 participants per treatment arm (Casagrande et al, 1978).

A total of 396 participants (198 per arm), rounded up to 400 participants (200 per arm) is required to account for an estimated rate of randomised participants who won't be valued for the primary analysis of 30%.

[redacted]

2 GENERAL INFORMATION

2.1 Background details

All study data will be transferred to a SAS database (version 9.4 or later, SAS institute, North Carolina, USA) for statistical analysis purposes. Data will be imported from a Data Capture System IBM Inform via validated SAS programs.

The SAP will be finalized before the interim analysis, any changes needed after the DMC meeting will lead to an SAP amendment which needs to be finalized before database lock and unblinding after agreement with the Sponsor on subject disposition and coding.

[redacted]

[redacted]

Deviations from the protocol will be judged during the study and/or when an individual participant's CRF is completed (monitored).
Before unblinding the data, a blinded data review meeting (BDRM) will take place where protocol deviations will be classified (major/minor protocol deviations) for statistical analysis. Intake of pain medications such as acetylsalicylic acid and metamizole, will not be considered a major protocol deviation.

2.3 Individual protocol deviations

Apart from violations of in- or exclusion criteria, no individual protocol deviations have been determined a priori.

A detailed review of all documented and derived deviations from protocol will be part of the blinded DRM before database lock. During this DRM the impact of protocol deviations on the analysis will be assessed and the conclusions recorded.

A complete listing of documented and derived protocol deviations and the judgment for assessment of subject disposition will be signed before database lock. A description of protocol violations that led to exclusion from any analysis sets will be included in the table part of the CSR.

3 ANALYSIS POPULATIONS

In general, the disposition of subjects will be displayed for the subject populations defined below.

Membership of subjects will be decided upon in a blind DRM with the Sponsor before database lock. The proper flag for analysis sets exclusion (e. g. exclusion from PP set), will be included in the analysis datasets. The protocol deviation list should be finalized before database lock.

3.1 Randomized Set

The randomized set includes all participants who were randomised.

3.2 Safety Set

The safety set (SS) includes all participants who received at least one tablet of the study drug (ivermectin or placebo).

3.3 Full Analysis Set

The Full Analysis Set (FAS) includes all participants randomly assigned to a treatment group having received at least one tablet of the study drug (ivermectin or placebo) and having at least one efficacy assessment after randomisation.

3.4 Modified Full Analysis Set

Modified FAS (mFAS) includes all FAS participants with a confirmed negative SARS-CoV-2 RT-PCR test at baseline.

3.5 Per-protocol Set

The Per-Protocol Set (PPS) is a subset of participants in the mFAS who did not present major deviations from the trial protocol.

The primary efficacy endpoint will be analysed using the mFAS and the PP set. The PP analysis will be considered as a sensitivity analysis.

Secondary efficacy endpoints will be analysed using the FAS or mFAS and PP set.

In case of dispensation/randomisation major error (i.e. the participant did not receive the treatment planned by the randomisation), in agreement with the intention-to-treat (ITT) principle, participants in FAS and mFAS analyses will be analysed in the group planned by the randomisation and not “as treated”. As treated analyses will be performed as sensitivity analyses only if the frequency of major dispensation/randomisation error is greater than 10%.

The safety set will be used for safety analyses. In case of dispensation/randomisation major error the safety analyses will be performed “as treated”, according to the real treatment received by the participant.

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4 STATISTICAL ANALYSES

All statistical analyses will be performed using the SAS® software (Version 9.4 or later, SAS institute, North Carolina, USA).

All descriptive statistics will be given by treatment group. For baseline and basic variables, they will also be given for the entire analysis set. Screening failure data will not be analysed.

If not stated otherwise the following standard types of descriptive analyses will be presented:

- Descriptive statistics for continuous data

N, mean, SD, min, lower quartile, median, upper quartile, and max will be presented. These descriptive statistics will be determined for measured values and optionally for differences to baseline.

- Descriptive statistics for categorical data

  Absolute frequencies and percentages will be presented. Percentage bases (denominators) will be identified in the table title or footnote (i.e. all subjects at risk, all cases). For changes from baseline, shift tables may be generated.

- Inferential statistics

  Unless otherwise stated, all statistical tests will be performed two-sided and at a type I error probability of α=0.05.

  Unless otherwise stated, all confidence intervals (CIs) will be derived two-sided and at a confidence probability of 1-α=0.95.

- Listings

  All recorded data will be listed by subject sorted by treatment group. Identification variables are centre number, participant number and treatment.

Derived data will be stored in special analysis data sets and will be calculated as outlined in section 6.1.

4.1 Conventions

4.1.1 Baseline definition

Results obtained on D1 (Screening/Randomization) of the study are considered as baseline results. In case of more than one result the closest to start of treatment will be used.

4.1.2 Missing data

In general, an observed cases approach will be applied in case of missing data, i.e., only the observed subject data at a given timepoint will be used.

There will be one notable exception to this rule for the primary efficacy endpoint: if a subject discontinued the study without a confirmed negative test result on D28 (and on any day in between), then the missing data will be imputed using a multiple imputation (MI) method, under the assumption that the results are missing at random (MAR). Details on the MI method can be found in section 4.6.1. The MI method will only be used for the primary efficacy endpoint.

Missing/incomplete information related to AEs and concomitant medications will be handled as listed below, when applicable. Following these steps using temporary programming will ensure that missing date imputation uses the most conservative approach.

In case of a (partially) missing onset date, and the end date is determined to be after the first date of study drug administration, the onset date will be imputed as follows:

- Partially missing onset date:

- If the day part is missing and month is equal to month of first study drug administration, then day will be set to day part of first study drug administration date.
- If the day part is missing and month is not equal to month of first study drug administration, then day will be set to the first day of that month.
- If both day and month part are missing, and year is not the same as the year of the first study drug administration, then day and month will be set to 1 January.
- If both day and month part are missing, and year is the same as the year of the first study drug administration, then day and month part will be set to day and month of first study drug administration.

- Complete missing onset date:
  - If the end date is on or after date of first study drug administration, then the onset date will be set to the date of first study drug administration.
  - If the end date is prior to the date of first study drug administration, then the onset date does not need an imputation, and the event or medication is considered a pre-treatment AE or prior medication.

In case of a (partially) missing end date, the end date will be imputed as follows:

- In case end date is partially missing:
  - If the day part is missing, and the month and year present then day will be set to the last day of the month or the end of study date, whichever is earliest.
  - If both day part and month part are missing and year is the same as the year of the end of study date, then day and month will be imputed with the end of study date.
  - If both day part and month part are missing and year is prior to the year of end of study, then day and month will be set to 31 December.
- Completely missing end date:
  - If the outcome of the AE is not marked as recovered/resolved:
    - The event will be assumed to be ongoing.
  - If the outcome of the AE is marked as recovered/resolved:
    - The end date will be imputed with the end of study date.

In case both onset and end date are missing, the onset date will be imputed with the date of first study drug administration and the end date with the end of study date and the AE will be considered treatment emergent.

AEs with missing severity/relatedness will be considered severe/related.

Note that imputed dates will not be presented in the listings but will only be used in duration and onset time calculations, descriptive statistics and/or statistical analysis.

For additional standards and conventions applied in the generation of statistical outputs please refer to section 8.

4.2 Demographic and other background data

4.2.1 Basic description

The disposition of subjects (cf. Section 3) will be tabulated by treatment and for the entire analysis set (pooled treatment groups). Frequencies of different reasons for exclusions (based on defined PD categories) from analysis sets will be listed.

Similarly, discontinued subjects will be described by frequencies of reason for termination and in individual listings.

The following background data will only be listed:

- Details on medical/surgery history
- Eligibility

4.2.2 Homogeneity tests

Homogeneity tests between treatment groups will be performed for age, sex, height, body weight and BMI.

4.3 IMP exposure, compliance

Treatment compliance will be described per visit by descriptive statistics on:

- Number of participants with modified, interrupted or missed study treatment with reasons
- Number of missed doses
- Number of days without medication
- Number of tablets returned

4.4 Medical history

Medical history terms will be coded using the MedDRA dictionary, with version as documented in the Data Management Plan and presented descriptively by system organ class and preferred term. Details will be listed.

4.5 Prior and concomitant medication

"Concomitant" is defined as a medication which is taken during study treatment (starting before or during) and will be coded according to the WHO Drug Dictionary. Summary tables will be presented by international non-propriety name (INN) and WHO drug label.

Prior medication is defined as medication taken prior to the first dosing of study drug, i.e., the end date is before the first study drug intake.

Any medication with a missing start date will be considered 'concomitant', unless a (partial) end date shows that the medication is stopped prior to first study intake, then it will be considered as prior medication.

Medication with a missing end date will be considered continued during the study and should be considered as concomitant, unless a (partial) end date shows that the medication was stopped before the first study intake.

4.6 Efficacy

4.6.1 Primary endpoint

The primary endpoint is the proportion of laboratory-confirmed COVID-19 infections between baseline and Day 28. Frequency tables will be provided, and individual results will be listed.

For missing results of the primary endpoint, the multiple imputation (MI) method will be used. MI is performed using 3 general steps: imputation, analysis, and pooling. A total of 10 multiple imputations will be generated using a fully conditional specification (FCS) regression. This method conditions on observed values of the primary outcome measured at other time points (including baseline measurements) and possible other covariates that are related to the missing data pattern and/or primary endpoint. Furthermore, imputations will be performed in each treatment group separately and, if applicable, by stratification factor. The statistical model will be applied to each imputed dataset separately. The estimated parameters from the models will then be pooled using Rubin's combining rules. It should be noted that these combination rules rely on the assumption that the estimated

statistics are approximately normally distributed, which may not be the case for the underlying data. Normalizing transformations will then be used on the estimated statistics prior to applying Rubin's rules.

The comparison between the two treatment groups of the proportion of participants will be performed using the Cochran Mantel Haenszel (CMH) chi-squared test. Odds-ratio, relative risk and risk differences and corresponding 95% CI will be reported. Country will be used as a stratification factor. In case the study was only performed in one country, the Chi-squared/Fisher's exact test will be used.

This analysis will be performed based on the mFAS and PP population using the planned treatment.

4.6.2 Secondary endpoints

[redacted]

The analysis of the secondary endpoints is purely explorative.

Results of RT-PCR tests and time to a positive test will be performed on the mFAS and PP population, while the analysis related to the occurrence of symptoms, (related) adverse events are performed on the FAS and PP population.

Treatment comparisons on proportions will be done using Cochran Mantel Haenszel chi-square test presenting odds-ratios, relative risk, and risk differences with 95% confidence intervals. Country will be used as a stratification factor. In case the study was only performed in one country, the Chi-squared/Fisher's exact test will be used.

Comparisons between treatment groups on time to events will be done by using a Cox proportional hazard model, under the assumption of proportional hazards. Time-to event curves will be created for visualization. Hazard ratios with 95% CI will be presented, together with the P-values. Censoring will be at study completion or at discontinuation date (including date of death, if occurring).

Treatment comparisons on mean score (WHO COVID-19 and NEWS-2) will be performed per time point by means of the t-test. If normality cannot be assumed based on visual inspection, a non-parametric alternative will be used.

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Treatment comparisons on durations will be examined by means of the non-parametric Wilcoxon-Rank-Sum test. If normality can be assumed based on visual inspection, a parametric alternative will be used.

4.6.3 Further Exploratory endpoints

Factors that may affect the SARS-CoV-2 infection or COVID-19 disease such as sex, age, BMI, and SARS-CoV-2 variant type will be assessed with a logistic regression model with proportion of COVID-19 infections as dependent variable and treatment as independent variable and the factors as covariates. Odds-ratios, 95% CI and P-values will be presented.

4.7 Safety

All safety analyses will be based on the SS population according to the actual treatment the participant received.

4.7.1 Adverse events

Adverse events will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). Coding of verbatim terms has been performed either by Ergomed or the Sponsor and that all relevant codes are stored in the database.

Adverse events will be classified according to period of occurrence: pre-treatment AEs, treatment-emergent AEs (TEAEs) and post-treatment AEs (PTAEs).

- Pre-treatment AEs are defined as adverse events starting before the first study drug intake.
- TEAEs (i.e. during the treatment period) are defined as AEs starting from the first study drug intake until three days after the last study drug intake.
- Post-treatment AEs are defined as AEs starting four days after the treatment period (last study drug intake).

AE reporting will focus on TEAEs and PTAEs. Pre-treatment AEs will only be listed.

Frequency tables of participants experiencing at least one occasion of the event while at risk (along with the number of different occurrences of the TEAE), will be presented for the following types of adverse events:

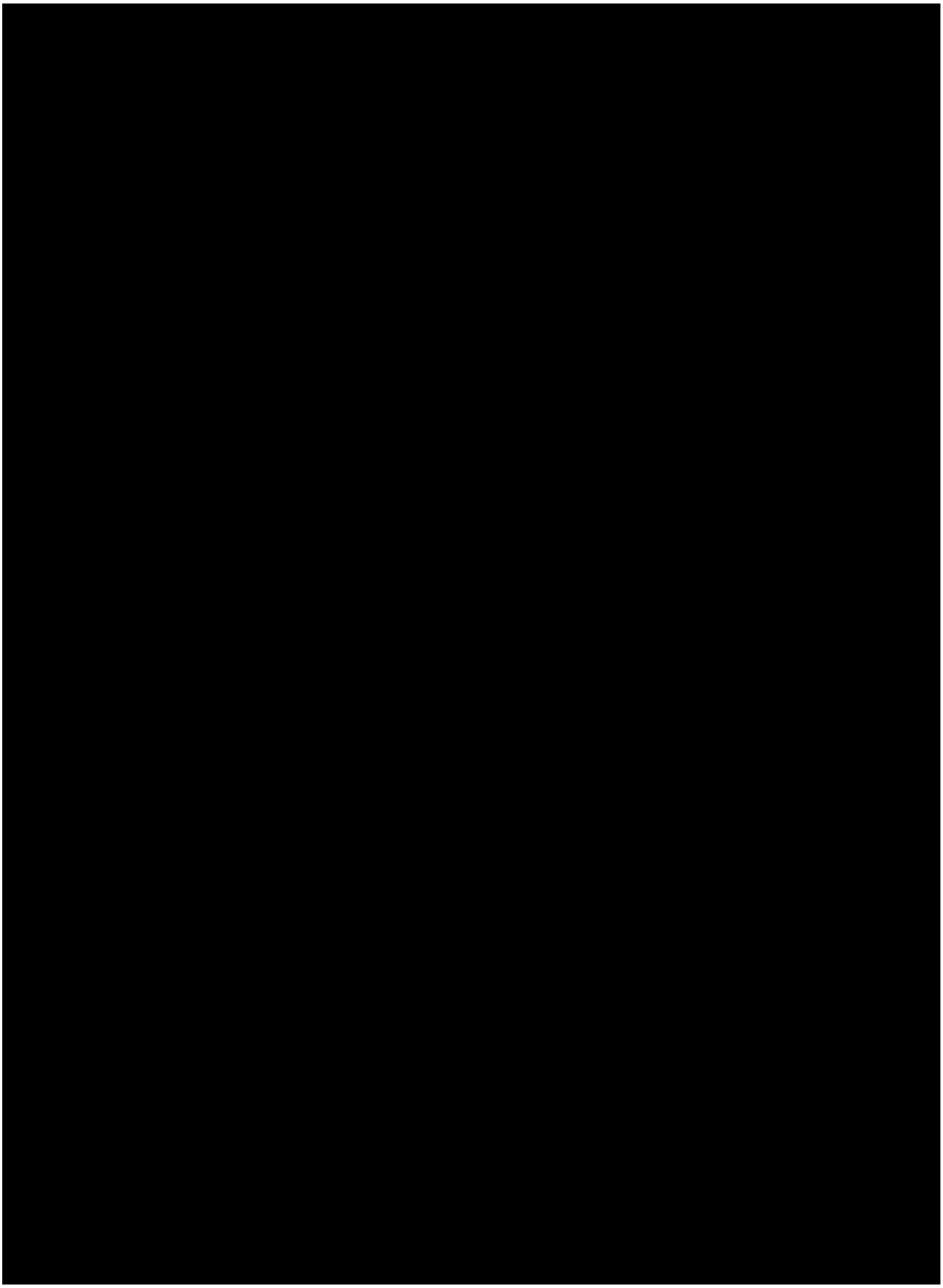
- All TEAEs and PTAEs irrespective of the causality assessment
- TEAEs and PTAEs by CTCAE grade
- TEAEs and PTAEs by action taken with the study medication
- Related TEAEs and PTAEs
- Serious TEAEs and PTAEs (SAEs)
- Related serious TEAEs and PTAEs
- Fatal TEAEs or PTAEs

Participants will only be counted once within a PT or SOC.

SOC terms will be presented according to the Internationally Agreed Sorting Order (MedDRA).

Comparison between the treatment groups on the number of participants with TEAEs/PTAEs will be performed by means of a Fisher's exact test.

Detailed listings of all fatal and other serious events will be provided (for section 14.3.2). Narratives will not be included in section 14.3.3 but will be provided by medical writing in section 12.3.2 of the CSR. All adverse events (i.e. TEAEs as well as non-treatment emergent events) will be listed in section 16.2 of the CSR. However, only TEAEs and PTAEs will be summarized in the tables.



5 QUALITY CONTROL

The SAP will be reviewed by the trial statistician (TS) before signature. Particularly the TS has checked the consistency of the described methods and outputs with the actual version of the study protocol. In addition, a sponsor representative has reviewed the SAP before final approval.

Log files of all SAS® programs used in the analysis will be checked for errors, warnings and suspicious notes by the statistical programmer. All findings will be either eliminated or commented upon. The final version of each program will be stored along with its log file in the electronic archive.

All programs will be validated by an independent statistician or statistical programmer depending on the requested validation level selected in the List of TLFs form (FRM/BS/001.02) for a particular program.

The agreement of the program outputs with the SAP, their consistency and plausibility will be checked by the TS. Moreover, the TS will review the outputs regarding completeness, readability and comprehensibility.

The described process is associated with the 'normal' level of program validation. Additional levels of quality control can be specified in the List of TLFs (see Appendix, 1) for individual outputs.

For the interim analysis, an unblinded statistician will be involved in the validation of the output and/or programs.

[redacted]

7 REFERENCES

No specific references were used.

8 STANDARDS USED IN PREPARATION OF STATISTICAL OUTPUTS

The below conventions will be followed as agreed with the Sponsor.

8.1 Programming

- One SAS program should create only one output.
- One output file can contain different output types (e. g. descriptive and inferential).
- Individual output files will be created in MS Word format (Rich Text Format, RTF).
- Once delivered to the client, numbering of TLFs will not be altered, unless agreed with the client.

8.2 Layout

- TLFs will be produced in landscape format
- TLFs will have a minimum 2 cm on every side
- TLFs will be produced using the Courier New font, size 8
- Section numbering of TLFs will follow ICH E3 guideline.
- Numbering of TLFs will follow the convention XXX-YY, where XXX stands for a (sub-)section number of the ICH E3 guideline and YY represents the sequence number of the output within the section. A dash (‘-‘) will always be used to separate section numbers from output sequence numbers
- Titles and footnotes for figures will also be in Courier New font, size 8.
- Tables and listings will be in black and white (no colour), figures may include only colour that can be distinguished when printed on a grey-scale printer
- Text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will be used sparingly in the TLFs
- The ANSI character set will be used in the TLFs. Certain subscripts and superscripts (e.g., m^2, AUC_{norm}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, unless they are derived directly from the data

8.3 Headers, Titles and Footnotes

- All output will have the following header at the top left of each page showing the study ID, the date of output generation and an internal pagination, where Y stands for the total number of pages in the pertaining output.

- Also, all TLFs will have the following footer, identifying the generating SAS program (XXX.SAS), a reference to the relevant subject listing and the date of the data snapshot:

```
SAS program: <XXX>.sas          Ref. list X.X.X-YY          Data status: YYYY-MM-DD
```

- Each TLF will bear a title which is repeated on each page of the output.
- The title at the top of the page will be horizontally cantered in bold font.
- A blank line will separate the title from the body of the output.
- The title will consist of an Output number, a descriptive title and a description of the presented analysis set (if applicable).
- The title will have the following general appearance:

```
Table / Figure / List XX.X.X-YY
   Descriptive Title line 1
   Descriptive Title line 2
(All subjects in the FAS, N=nnn)
```

- Each new footnote should start on a new line, where possible.
- Preferably, footnotes should be left justified. When extending beyond a single line, a manual linefeed should be inserted to avoid meaning distortion.
- An automatic footnote '(continued)' will appear at the bottom of TLFs that extend over more than one page.

8.4 General Conventions

- For measured variables column headers should include the unit in their description
- The order of treatment arms in the TLFs will be consistent throughout the entire TLF presentation
- Alphanumeric values are preferably displayed left-justified;
- Dates are presented left-justified
- Integer numbers (e.g., counts) can be centred or right-aligned
- Numbers containing fractional portions will be decimal-aligned.
- Fractional numbers with absolute value less than 1 will carry a leading zero, i.e. 0.123 not .123.
- Units of measured or derived variables will be included where appropriate
- Unless otherwise warranted, the estimated mean, median and quartiles for a set of values will be displayed with 1 more significant digit than the original values, and standard deviations with 2 more significant digits. The minimum and maximum should report the same significant digits as the original values.

- P-values are output in the format: “0.xxxx”, where xxxx is the value rounded to 4 decimal places. P-values less than 0.0001 will be presented as <0.0001.
- Precision of percentages displayed will depend on the total study size. For studies with less than 1000 subjects values will be presented with one decimal place. For studies with more than 1000 subjects, values will be presented with two decimal places.
- Tabular display of data for medical history, prior/concomitant medications and all tabular displays of adverse event data are generally presented by body system, treatment class, or SOC according to the Internationally Agreed Sorting Order of the MedDRA, unless otherwise agreed.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis (sub-) population presented.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, an explanatory text will be added to clarify that multiple answers were possible.
- Missing values will be displayed either by a double-dash (“--”) or as “NA” (=’not available/applicable’), whichever is appropriate.
- Dates are displayed in according to ISO date/time format as YYYY-MM-DD, e. g. 2010 03 24. Missing dates may be represented as “NA”, if not available/applicable.
- Clock times are displayed as HH:MM or HH:MM:SS based on 24-hour clock