Protocol Number: AV-APL-B-002-22

Official Title: A Multicentre, Open label, Randomised, Controlled, Basket, Pragmatic, Phase II, Clinical and Translational Study to Determine the Efficacy and Safety of Plitidepsin versus Control in Immunocompromised Adult Patients with Symptomatic COVID-19 requiring Hospital Care (NEREIDA)

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Statistical Analysis Plan (SAP)

Protocol Title:	A Multi-centre, Open-label, Randomised, Controlled, Basket, Pragmatic, Phase II, Clinical and Translational Study to Determine the Efficacy and Safety of Plitidepsin versus Control in Immunocompromised Adult Patients with Symptomatic COVID-19 requiring Hospital Care (NEREIDA)
Protocol Version No./Date:	Version 3.0 - 22 MAR 2023
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1.0 Approvals

Sponsor	
Sponsor Name:	Pharma Mar, S.A.
Representative/ Title:	[redacted]
Author:	[redacted]
Signature /Date:	[redacted]

(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
1.0	Created as new
2.0	Protocol has been updated to correct some errors detected and to implement some changes in response to clarifications requested by different drug agencies from the countries where the NEREIDA study is going to be carried out After IDMC Organizational meeting held on 22Feb23 some requests/clarifications have been also added. After agreement, Bayesian analyses will be performed by another CRO 'Phastar'.
3.0	Due to low recruitment, early study closure has been decided on 23Feb24. Therefore, SAP is abridged to provide the essential results for an abbreviated Clinical Study Report.

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the abbreviated reporting and analyses of data collected under PharmaMar Protocol AVL-APL-B-002-22.

5.0 Scope

The Statistical Analysis Plan outlines the following:

- Study Objectives
- Study Design
- Study Estimands
- Applicable Study Definitions
- Statistical Methods

6.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). Any further changes to the protocol or CRF may necessitate updates to the SAP. A first version of the SAP is expected prior to first patient in (FPI) and final approval of the SAP will occur prior to database lock. Due to low recruitment, early study closure was held on 23Feb24. Therefore, SAP is abridged to provide the essential results for an abbreviated Clinical Study Report (CSR) where information related to safety and descriptive efficacy results will be described. Study objectives, endpoints and populations will be adapted accordingly in order to present the most relevant data.

Consequently, no formal statistical significance tests will be presented, although the descriptive tables will allow a numerical comparison of the characteristics and outcomes of the patients in the experimental and control arm across the subgroups.

7.0 Study Objectives

7.1 Primary Objective

To evaluate efficacy of plitidepsin in pre-specified groups of immunocompromised patients with symptomatic COVID-19 requiring hospital care vs control in terms of mortality.

7.2 Key Secondary Objective

To describe efficacy of plitidepsin and the control in terms of viral clearance, in each group.

7.3 Secondary Objectives

- Efficacy secondary objectives
    - To describe efficacy of plitidepsin and the control in terms of sustained end of hospital care, in each group.
    - To describe efficacy of plitidepsin and the control in terms of symptomatic improvement, in each group.
    - To describe efficacy of plitidepsin and the control in terms of clinical status (11 category WHO Clinical Progression Scale), in each group.

  - To describe efficacy of plitidepsin and control in terms of the need of any kind of supplementary oxygen, in each group.

- Safety secondary objectives
  - To describe safety/tolerability of plitidepsin and the control in terms of adverse events, adverse reactions and mortality, in each group.
  - To describe safety/tolerability of plitidepsin and the control in terms of abnormal laboratory parameters, in each group.
  - To describe safety/tolerability of plitidepsin and the control in terms of variations of vital signs, in each group.
- Other secondary objectives
  - To describe efficacy of plitidepsin and the control in the need of any type of advanced oxygen support (high-flow nasal oxygen, extracorporeal membrane oxygenation (ECMO), or non-invasive or invasive mechanical ventilation), in each group.
  - To describe efficacy of plitidepsin and the control in the need of intensification of respiratory or intensive care support, in each group.
  - To describe efficacy of plitidepsin and the control in the need of intensification of pharmacological therapies for COVID-19, in each group.
  - To describe efficacy of plitidepsin and control in terms of superinfection, in each group.
  - To describe efficacy of plitidepsin and the control in terms of all-cause- and related to COVID-19-mortality, in each group.
  - To describe efficacy of plitidepsin and the control in terms of subsequent hospital admissions, in each group.
  - To describe efficacy of plitidepsin and the control in terms of the time course of viral load, in each group.
  - To describe efficacy of plitidepsin and the control in terms of the evolution of inflammatory markers, in each group.
  - To describe efficacy of plitidepsin and the control in terms of the immune response against SARS-CoV-2, in each group.
  - To describe efficacy of plitidepsin and the control in terms of radiological evolution, in each group.
  - To describe efficacy of plitidepsin and the control in terms of restoration of the therapy for the underlying disease, in each group.
  - To describe safety/tolerability of all pooled plitidepsin arms and all control arms in all the aforementioned endpoints (all objectives).
  - To compare efficacy and safety/tolerability between plitidepsin arms (across different groups). <Not applicable as sample size does not allow any kind of comparison>
  - To explore prognostic/predictive factors for clinical deterioration or mortality or drug response. <Not applicable as sample size does not allow any kind of comparison>

- To increase pharmacology knowledge of plitidepsin.

8.0 Study Design

8.1 Rationale

Coronavirus disease 2019 (COVID-19), produced by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), has caused a global pandemic.

- Immunocompromised patients are at increased risk for severe and fatal coronavirus disease 2019 (COVID-19) outcomes.
- Patients with immune-system disorders have not been sufficiently represented in the clinical trials for COVID-19 antiviral drugs.
- Concerns have been raised about whether the accepted clinical practice standard to treat COVID-19 with weak antiviral agents and immunosuppressive therapies may promote chronic infection and worse outcomes in immunosuppressed patients (at risk for protracted SARS-CoV-2 infection), including selection and transmission of new SARS-CoV-2 variants.
- Studies among immunocompromised hosts should ideally be focused on identifying direct-acting antivirals that markedly reduce SARS-CoV-2 replication, be they small molecules or antibodies.
- Evidence of potent antiviral activity of plitidepsin observed in vitro and/or in vivo.
- Plitidepsin anti-viral activity is “agnostic” to the different SARS-CoV-2 variants.
- There is no signal supporting clinically-significant immunosuppressive potential of plitidepsin neither in the context of oncology clinical safety analysis after the first infusion of treatment nor in the clinical COVID-19 development (APLICOV-PC study).
- The compassionate use of plitidepsin in immunosuppressed patients has shown:
  - Feasibility of plitidepsin in this target population of dismal prognosis.
  - Good tolerability of the 2.5 mg daily for three consecutive days.
  - Feasibility of a second salvage stint of plitidepsin in a small subset of patients with persistent viral load.
  - A median time to SARS-CoV-2 real time polymerase chain reaction (RT-PCR) negativisation of 17 days from plitidepsin Day 1.
  - A median time to oxygen independence of 13 days and, in line with this, significant radiological improvement of COVID-19 pneumonia, with exceptional requirement of high-flow oxygen intervention or intensive care unit, frequently limited in this patient population.

A full rationale for the study may be found in the appropriate sections of the study Clinical Protocol.

8.2 Overall Design

This is a multi-centre, randomised, controlled, open-label, pragmatic, phase 2 basket study to assess the efficacy and safety of plitidepsin in different groups of immunocompromised patients with coronavirus disease 2019 (COVID-19) who require hospital care.

More than 50 sites are planned to participate in this study worldwide.

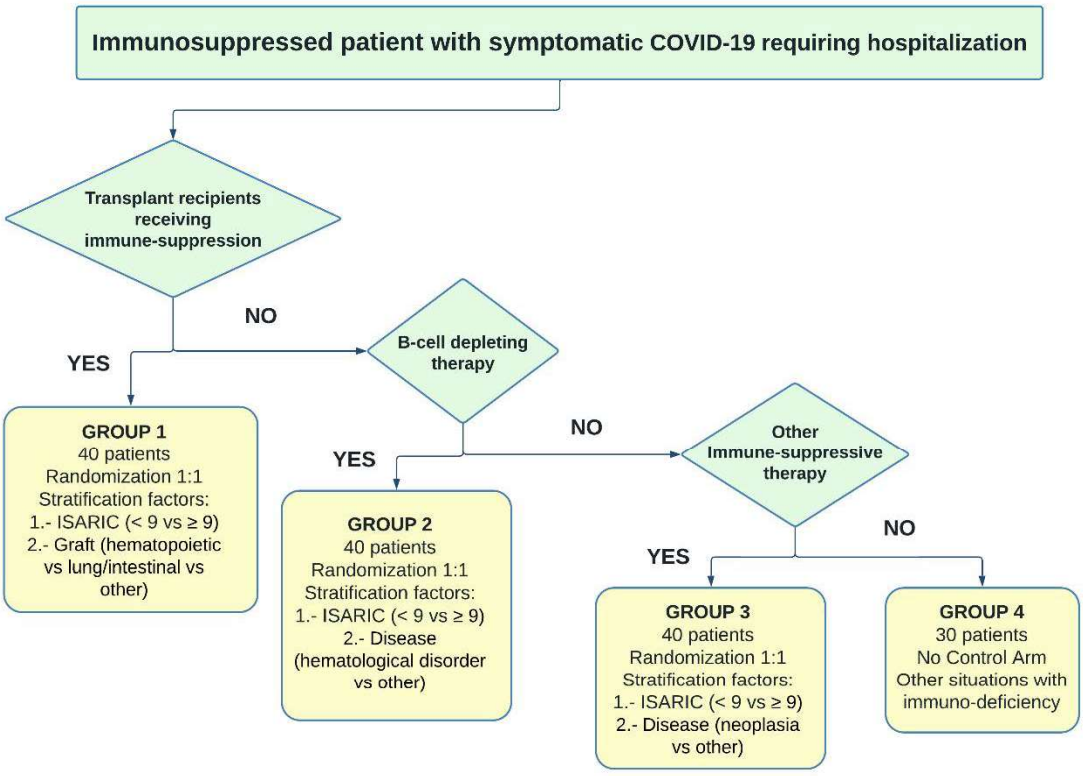
Approximately 150 patients are foreseen for the study, divided in 4 different groups of immunocompromised patients:

- Group 1 –Patients receiving immune-suppression due to haematopoietic or organ transplantation.

- Group 2 – Patients receiving B-cell depleting therapies.
- Group 3 – Patients receiving other immune-suppressive therapies.
- Group 4 – Other situations with immune deficiencies.

Whenever a patient can be allocated to more than 1 group, the priority will be group 1 > group 2 > group 3 > group 4. In groups 1, 2, and 3, patients will be randomised to receive best standard care (BSC) ± other antiviral (if clinically indicated) on control arm and BSC + plitidepsin on experimental arm. Group 4 will not be controlled (it was not applicable in Spain), as shown in Figure 8.2.1.

Figure 8.2.1. Algorithm for Patient Assignment in NEREIDA Basket Trial.



Stratification:

- Group 1: ISARIC mortality (<9/≥9) | Type of graft (allogeneic haematopoietic/lung or intestinal/other)
- Group 2: ISARIC mortality (<9/≥9) | Disease (haematological neoplasm/other)
- Group 3: ISARIC mortality (<9/≥9) | Disease (neoplasia/other)
- Group 4: Not applicable

Study periods:

The study will include a Screening period, a Treatment period and a Follow-up period.

Refer to the Schedule of Assessments (Protocol Appendix 13) for data to be collected.

The Screening period starts once the patient has provided written informed consent and ends when the patient is randomized (allocated in group 4) in the study. Parameters assessed during this time will serve as the baseline values. The screening procedures should be preferably performed within 24 h prior to administration of study treatment, allowing a maximum of 48 h prior to administration of study treatment if required.

The Treatment period starts on Day 1 (date of randomisation) to 24 h after the last dose of the antiviral therapy; if no antiviral was given in the control arm, then the treatment period will finish on Day 4, for data management purposes. Antiviral treatment must always be started on the randomisation date.

The Follow-up period starts after the end-of-treatment and lasts until the end-of-study.

The End of Study (EOS) is Day 60 (±3) or date of early study termination unless ongoing SAEs, if applicable.

The End of Trial (EOT) will be when the Last Patient Last Visit (LPLV) has occurred.

All patients will receive the best available care as per applicable local, institutional, national, supranational COVID-19 treatment guidelines.

Patients assigned to the experimental arms will receive, in addition, plitidepsin as a 1-h IV infusion, during Days 1 to 3.

Patients randomised to the control arm may receive a regulatory-approved antiviral treatment in addition to the BSC.

For prevention of infusion-related (i.e., plitidepsin-related) reactions (IRRs), allergic reactions and emesis reactions, administration of premedications is mandatory in the experimental arms.

All consenting patients discontinuing early from the study before the EOS visit should complete the early termination/withdrawal procedures.

Duration of Study Periods:

- Screening period: From the day of ICF signing prior to randomisation).
- Day 1: Date of randomisation. Treatment must be started on the same date.
- Treatment period: from Day 1 to 24 h after the last dose of the antiviral therapy; if no antiviral was given in the control arm, then the treatment period will finish on Day 4, for data management purposes.
- Follow-up period: From the end-of-treatment to end-of-study.
- EOS: Day 60 (±3) or date of early study termination unless ongoing SAEs, if applicable.
- Overall study duration: 60 (±3) days since randomisation.
- End of the trial will be when the Last Patient Last Visit (LPLV) has occurred.

Independent Data Monitoring Committee (IDMC):

An IDMC was established to provide study oversight. The IDMC was composed of individuals external not only to the Sponsor but also to the trial managers (including Sponsor's and Contract Research Organisation's [CRO] medical monitors) and study investigators.

Given the decision to terminate the study due to low accrual, the IDMC activity has been discontinued and there will not be distinction between blinded and unblinded procedures.

Study "Stopping rules"

The Sponsor may suspend or terminate the study if:

- New toxicological or pharmacological findings or safety issues that invalidate the earlier positive benefit-risk assessment occur;
- Significant safety concerns, according to the Sponsor's criteria, arise during the conduct of the study;
- The development of plitidepsin is discontinued;
- Any other reason (e.g., best interest of the patients, accrual rate makes the completion of the study feasible, etc.) leads to this suspension or termination.

The Sponsor has decided to terminate the study due to low accrual rate.

Blinding/Unblinding

For randomization purposes, no statistical personnel can access the RTSM Rave system.

For IDMC procedures, an independent team outside the scope of this SAP was created following the IDMC Charter.

For the clinical database, PharmaMar Biostats team remains blinded until the results of the analysis are released. Meanwhile, blinded outputs and datasets will be created by ICON Statistics & Programming department for PharmaMar. The procedure planned to blind data for dry-run review consisted of shuffling data and not including outputs with any CRF information where treatment arm is detailed (see below the specific CRF forms). However, given the early termination of the study, there is no risk of bias in the knowledge of randomization lists by the study personnel once the recruitment period has ended. Therefore, on 19/March/2024 it was decided to unmask data and continue with unblinded procedures.

8.3 Endpoints

Efficacy primary endpoint:

- 1-month† all-cause mortality rate. †(Day 30 since randomisation).

Key secondary endpoint:

- Time to confirmed negativisation in SARS-CoV-2 antigen test or RT-PCR Ct > 30.

Secondary endpoints:

Efficacy secondary endpoints

- Time to sustained end of COVID-related hospital care from the time of randomisation. Sustained discharge is defined as no subsequent admission within 30 days of initial end of hospital care [up to day 60 (±3)], related to either COVID-19 or COVID-19 therapy.
- Time to sustained improvement (defined in Protocol Section 7.1.3) and resolution of selected COVID signs/symptoms (See Protocol Appendix 10 - COVID-19 signs/symptoms checklist).
- Distribution of patients according to their clinical status by the 11-category WHO Clinical Progression Scale, at Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3) (See Protocol Appendix 1 – 11-Point World Health Organization (WHO) Clinical Progression Scale).
- Percentage of patients requiring oxygen therapy on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Time to sustained discontinuation (i.e., at least 7 days) of oxygen supplementation.

Safety secondary endpoints

Frequency of the following events (all-cause and drug-related):

- Treatment-emergent adverse events (TEAEs);
- TEAEs ≥ grade 3 according to the National Cancer Institute [NCI]-Common Terminology Criteria for AEs (CTCAE v.5.0);
- Adverse events of special interest (AESIs);
- Serious adverse events (SAEs);
- Drug related Serious Adverse Events (i.e., SARs);
- Adverse events leading to treatment discontinuation; and
- Deaths (COVID-19-related/all).
- Change respect to baseline* in individual study-defined laboratory parameters (See Protocol Section 5.7, 5.8 and 5.9 and Protocol Appendix 8 – Clinical Laboratory Analyses).
- Change respect to baseline* in individual vital signs (See Protocol Section 5.7, 5.8 and 5.9).

*Baseline = latest test performed between screening and drug administration

Other Secondary/Exploratory Endpoints

- Percentage of patients requiring advanced oxygen support on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2,) and 60 (±3).
- Time to intensification of respiratory support (WHO >5) (See Protocol Appendix 1 – 11-Point World Health Organization (WHO) Clinical Progression Scale).
- Total duration of advanced oxygen support.
- Percentage of patients requiring high-flow oxygen on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Total duration of high-flow oxygen therapy per patient.
- Percentage of patients requiring non-invasive mechanical ventilation on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Total duration of non-invasive mechanical ventilation per patient.
- Percentage of patients requiring invasive mechanical ventilation or ECMO on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Total duration of invasive mechanical ventilation or ECMO per patient
- Percentage of patients requiring admission to intensive care unit (ICU) on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Total duration of ICU stay.
- Time to onset of additional (i.e., not present at baseline) immune-modulating drugs.
- Percentage of patients receiving immune-modulating drugs on Days 1, 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Time to onset of additional (i.e., not present at baseline) antiviral drugs.
- Percentage of patients receiving subsequent antiviral drugs (i.e., not present at baseline) on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Percentage of patients with a new infection by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).
- Cumulative mortality (all-cause and related to COVID-19) by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).

- Percentage of patients in each study group who require subsequent admission within 30 days of initial end of hospital care [up to Day 60(±3)], related to either COVID-19 or COVID-19 therapy.
- Change respect to Day 1 in the viral load of SARS-CoV-2, measured by RT-PCR, by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), 45 (±2), and 60 (±3), in each study group.
- Percentage of patients in each study group with undetectable viral load, by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), 45 (±2), and 60 (±3).
- Time to either undetectable viral load of SARS-CoV-2 or > 2 logs reduction respect to Day 1
- Change respect to baseline* in inflammatory and immunological (C- reactive protein [CRP], procalcitonin, lactate dehydrogenase [LDH], ferritin, neutrophil-to-lymphocyte ratio, absolute lymphocyte count (ALC), D-dimer, and multiplex cytokines assay, by Day 4 (±1), 8 (±1), 15 (±1) and 30 (±2) and 60 (±3).
- Change respect to baseline* in individual serological assessments against SARS- CoV- 2, by Days 30 (±2), and 60 (±3).
- Change respect to baseline* in individual T-cell response against SARS-CoV-2 by Days 30 (±2), and 60 (±3).
- Change respect to baseline* to Days 15 (±2), and 30 (±2) in chest X-ray findings (Brixia score, centrally assessed) (Protocol Appendix 9 – Brixia Score).
- Percentage of patients requiring modification of the therapy (drugs, dose or schedule) for the underlying disease.
- Time in which pre-scheduled therapies for the control of the underlying disease were not able to be administered.
- Limited-sampling pharmacokinetics assessment (See Protocol Section 7.6).
- Pharmacokinetic(s)/Pharmacodynamic(s) (PK-PD) analysis

*Baseline = latest test performed between screening and drug administration

8.4 Randomisation

Patients will be sequentially allocated in their respective group, following the algorithm depicted in Figure 8.2.1.
Central randomisation will be implemented by means of RTSM Rave, for full details on how the randomization lists are created and block selection see the randomization plan. In groups 1-3, patients will be assigned to the experimental or the control arms at a 1:1 ratio. Stratification will be performed in the randomised groups. The ISARIC-4C mortality score will be used as a stratification factor in all groups (score <9/≥9). In addition, the type of graft (allogeneic haematopoietic/lung or intestinal/other) will be used for Group 1, whereas the underlying disease will be considered for Groups 2 and 3. For Group 2, the factor categories will be haematological neoplasm vs other disease; the respective categories for Group 3 will be neoplasia vs other. Stratification is not applicable in the non-randomised Group 4.
Day 1 is defined as the day of randomisation. Treatment must start within the same natural day.

8.5 Sample Size Calculation

A) Randomised groups (1-3)

Patients in three of the four groups will be randomly assigned to one of two arms. Each randomised group will have a sample size of 40 patients (20 in the experimental arm, 20 in the control arm).
Given the exploratory nature of this phase II study, this sample size has been chosen based on operational considerations to allow the feasibility of accrual in this relatively small population and also

provide preliminary estimates to establish an updated prior distribution of the mortality rates for further investigation using Bayesian methods in a potential Phase III study.
The operating characteristics of the calibrated Bayesian hierarchical model (CBHM) described by Chu and Yuan (1) have been investigated by means of the CBHM package from Yuan at MD Anderson Cancer Center (2), and with reference to the JAGS program running in R version 4.2.1 (3) on Microsoft Windows 10.
Within the CBHM simulations, 5000 Markov-chain Monte Carlo (MCMC) repetitions per scenario were simulated with a range of operating characteristics for the null, alternative and true mortality rates moving from 5% to 95% in steps of 5% (Table 1). A maximum sample size of 40 per randomised group was set through the CBHM simulations, which in turn determines whether there is a need for the total sample size to be allocated. Within all simulations, the full 120 patients were used, suggesting that this is the minimum sample size that enables decision-making. As an example, if the mortality rate in each group is 20% and we target a clinically meaningful absolute reduction of 12.5% in the experimental arm (H0=20%, H1=7.5%), and the assumed true mortality rate is 7.5%, the simulation demonstrates that a sample size of 40 per basket will allow for a posterior probability around 0.9 in each basket (i.e. 90% probability that the experimental arm is better than the control in each basket), ranging from 0.87 (when the data from the fastest basket is analysed) to 0.915 (at the end of the accrual of the last basket) (type I error rate= 0.05).

Table 1 Example of simulated posterior probabilities for sample size definition.

Mortality rate –control arm (null)	Mortality rate – experimental arm (alternative)	True mortality rate	Sample size per basket	Posterior probability 1st basket	Posterior probability 2nd basket	Posterior probability 3rd basket
20%	7.5%	7.5%	30	0.82	0.84	0.865
20%	7.5%	7.5%	40	0.87	0.88	0.915
20%	7.5%	7.5%	50	0.895	0.905	0.93
20%	7.5%	7.5%	60	0.905	0.925	0.97
20%	7.5%	7.5%	70	0.945	0.98	0.985
20%	7.5%	7.5%	80	0.96	0.985	0.985

B) Non-controlled group 4

Clinical conditions that cannot be classified into one of the 3 randomised groups will be pooled into a fourth group of 30 patients. As this group is likely to be characterized by high heterogeneity, it will not have a control arm and will provide safety data on plitidepsin.. A Fleming's phase II procedure with a 1-stage design has been used to estimate the sample size needed to rule out that plitidepsin induces drug-related SAEs in at least 35% of the patients (null hypothesis), and to confirm that the respective rate is 10 % or lower (alternative hypothesis), with a type I error of 0.05 and a power of 90%.
If at least 25 patients out of a total sample of 30 do not experience a drug-related SAE, the null hypothesis will be rejected.

8.6 Population Sets

Immunocompromised adult patients with symptomatic COVID-19 requiring hospital care.
Patients must fulfill all the inclusion/exclusion criteria to be eligible to participate in the study.

8.6.1 Replacement of Patients

No patients will be replaced. For each group 1-3, all efficacy analyses will be done on Full Analysis Set (FAS) population (See 8.6.2.1 below).

Therefore, accrual in each group will end when the target number of evaluable patients in the FAS population has been reached.

8.6.2 Populations

The design of the trial, the Bayesian analysis and the sample size is based on the 30-day (+/- 2 d) survival information on the FAS population. The analysis of the primary and other time-to-event efficacy endpoints will be performed primarily in the FAS but also in the Per Protocol and 'As treated' populations. Supportive analyses will be performed on the Per Protocol (PP) population. Safety endpoints analyses will be based on the "As treated" population (also known as safety population). If there is any patient randomized by error in a different cohort that its correspondent cohort, for the analysis this patient will be moved programmatically to the valid one.

8.6.2.1 Full Analysis Set (FAS) Population

All randomised patients who have taken at least 1 dose of study treatment (plitidepsin or control) and have completed follow-up for survival until day 30 (±2). Patients who die before the end of follow-up period will also be included in the FAS population. FAS population will be analysed according to their randomised treatment arm.

8.6.2.2 As Treated Population

All patients who received any exposure to study treatment (plitidepsin or control). As Treated population will be analysed according to the treatment they actually received.

Day 1 therapy is defined as any exposure to study treatment (partial or complete).

<NOTE: Due to the premature study closure no PP specific outputs or sensitivity analyses will be generated in populations other than the FAS for baseline and efficacy analyses and safety population for safety analyses>.

9.0 Conventions and Derivations

Variables reported with different units will be homogenized to standardized variables following the International System of Units (e.g. laboratory tests, biometrical assessments...) unless otherwise specified.

By default, all results will be rounded to one decimal place, except when variables are integer, which will be reported without decimals (e.g., age in years). Percentages for 0 counts will not be presented and 100% values will be presented with no decimal places. For representing p-values four decimals will be selected as default but they could be rounded to fewer decimals if necessary.

Missing values will not be included in the calculation of outputs. Unless otherwise noted, missing data will not be imputed or carried forward.

For patients who discontinue treatment due to adverse events (related or not to study treatment) every effort should made to remain under study follow-up, anyway, if information is lost before day 28 the conservative value of death will be also imputed.

Patients with no available data for any time-to event efficacy endpoint will be censored at time 0. EOS: Day 60 (±3) or date of early study termination, if applicable. Patients not yet achieving the time to event endpoint will be censored at the last valid assessment prior to EOS. Efron's method will be used to handle ties.

Assessment windows as specified in the clinical protocol will be respected, see protocol Appendix 13 'Schedule of Assessments and Procedures' for definitions of trial days. Baseline is defined as latest test performed between screening and drug administration.

Change from baseline (%) is defined as: (test value-baseline value)/baseline value x 100.

9.1 Imputation in Incomplete Dates

Dates of certain historical or current clinical activities are key component for statistical analysis. An incomplete date results from a missing day, month or year; in that case, the missing figure can be imputed allowing for the calculation of variables, such duration and time to certain event. However, when all of them, day, month and year, are missing no imputation will be done.

Before randomisation/treatment start date
All variables needed to summarize for example prior information where partial information is available will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month is also unknown then the imputed date will 1/July. This assumption will be valid if the imputed date is earlier than the randomisation date; otherwise, the imputed date will be the first day of the month of the randomisation date (i.e. 01/Randomisation month date/year).
Between treatment start and end of treatment
All date variables during treatment where information is needed and is not fully available, for example adverse events or concomitant medications, will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month and/or year is also unknown then the imputed date will be 1/January (this assumption will be valid if the imputed date is earlier than the treatment start date; otherwise, the imputed date will be the treatment start date). For treatment emergent AEs/CMs a conservative approach will be taken and if imputed date may be considered treatment emergent or medication taken on treatment then always will be counted.
After end of treatment
A conservative approach for the variables collecting information after end of treatment where partial information is available will be imputed by means of SAS programming. The following rules will be implemented: if the day of a date is unknown then the imputed day will be 1; if the month is also unknown, then the imputed date will be 1/July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the last drug administration date plus 1 day.

10.0 Independent Data Monitoring Committee

An IDMC was established to provide study oversight. The IDMC was established and operated in compliance with the FDA Guidance for Industry "Establishment and Operation of Clinical Trial Data Monitoring Committees".

A separate IDMC charter has been written in order to specify the whole IDMC study conduct.

11.0 Statistical Methods

Non-continuous variables will be described in frequency tables using counts and percentages. Continuous variables will be described by median, mean, standard deviation (STD), interquartile range (Q1-Q3),

minimum and maximum. Study endpoints will be summarized by means of tables, listings for all CRF variables and figures for temporal series as viral load, lymphocytes/neutrophils evolution, LDH, CT>30 or oxygen necessities as well as Kaplan-Meier figures, as inverse KM (see section 11.8) where time to event data Y-axis started from 0% instead the usual 100%, e.g. time to confirmed negativisation in SARS-CoV-2 antigen test or RT-PCR Ct > 30, will be shown.

11.1 Subject disposition

Main characteristics concerning inclusion in the study, randomisation, enrolment by country/site, end of treatment and withdrawal of the study will be displayed in this section.

11.2 Demographic and Baseline Characteristics

Baseline data such as for example demographics, medical history, clinical evaluation will be described in the FAS population.

For pre-treatment characteristics with multiple measurements per patient before the start of treatment (e.g. laboratory assessments, vital signs), the baseline measurement will be considered the last value prior to or on the first day of treatment. Continuous variables that will be also presented as categorized summaries.

Age at informed consent will be summarized as continuous variable and categorized as <65y, >=65-74y and >=75y. Gender, race, stratification factors from eCRF randomization forms and from their corresponding eCRF forms, physical examination form including height, weight, BMI and abnormal results, respiratory assessments form including oxygen therapy status, SpO2, FiO2, SpO2/FiO2, PaO2 and PaO2/FiO2,vital signs form including systolic blood pressure, diastolic blood pressure, pulse and respiratory rate, ECG Test Results - Local Reading form including heart rate, PR interval, QRS duration, QT interval, QTcF interval (Fridericia's formula) and QTcF (ECG measurements will be taken in triplicates but average values will be shown by visit), SARS-CoV-2 Test, COVID 19 Vaccination, duration of the infection prior to study entry defined as time from currently COVID-19 episode diagnosis date to randomization as continuous variable and categorized as <5 days and >=5 days and any additional variable considered as clinically relevant.

11.3 Treatment Administration

Treatment compliance defined as the extent to which patients take medications as requested in the protocol will be measured as duration in days of antiviral exposure ((Last exposure date-First exposure date)+1), total number of infusions/doses administered, the number of infusions/doses where total amount was administered, the number of infusions/doses where total amount was not administered and the number of infusions interrupted will be listed and summarized using descriptive statistics where applicable.

11.4 Protocol Deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial. The study specific Protocol Deviation Guidance Document defines all important protocol deviations.
The study team will conduct on-going reviews of the deviation data and document must be finalized prior to database lock.
Summaries of protocol deviations will be produced.
Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio.

Below examples of deviation’s classification are listed.

Table 2 Important protocol deviations.

Category	Sub Category	Project Specific Protocol Deviation
Study Conduct/ Procedures	Inclusion/ Exclusion Criteria	Failure to complete or comply with inclusion/exclusion criteria
Study Conduct/ Procedures	Screening	Non-compliance with screening procedure protocol requirements to confirm eligibility of the patient
Study Conduct/ Procedures	Study Restrictions/ Withdrawal	Non-compliance with protocol restrictions (e.g. use of prohibited medication or prohibited treatment therapy)
Study Conduct/ Procedures	Dose Formulation/ Dose Administration	Administration Use of prohibited medication
Study Conduct/ Procedures	Dose Formulation/ Dose Administration	Incorrect study drug dose, frequency, timing or method of drug delivery (e.g. subject overdosed with study drug, incomplete study drug administered), incorrect volume of infusion
Study Conduct/ Procedures	Dose Formulation/ Dose Administration	Study drug dosing adjustments performed outside of Protocol

All-important protocol deviations leading to exclusion from any population occurring during the study will be reviewed and approved by Pharma Mar prior to database lock.

11.5 Concomitant medications and procedures

Concomitant medication [Anatomical Therapeutic Chemical – World Health Organization (ATC-WHO) coded by means of WHODrug dictionary] will be described. The number and percentages of patients using at least one medication will be displayed according ATC1/ATC2/ATC4/Term. Any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF and coded by Medical Dictionary for Regulatory Activities (MedDRA).

Administration of all concomitant drugs received prior the first drug administration or by the patient during the study must be reported in the appropriate section of the eCRF along with dosage information, dates of administration and reasons for use. Additionally, any unplanned diagnostic, non-diagnostic procedure, therapeutic or surgical procedure performed during the study period must be recorded in the eCRF.

11.6 Efficacy Analyses

This is an exploratory basket study to adequately approach the potential heterogeneity of clinical conditions included under the concept of immune compromise. The study implements a Bayesian methodology taking into account the relative low frequency of the conditions under study, the relative absence of prospective data of the outcomes of COVID-19 for the study populations (most of the available data are retrospective and belong to the early waves of the pandemic, with different viral variants than nowadays), along with the changing medical practices in these settings. Under these premises, a Bayesian approach is more appropriate in terms of efficient decision-making process, and will provide novel information for future therapeutic development in these clinical conditions (4).
The trial will use a minimally-informative prior of N(0,1) to update the information provided by the trial data to produce a posterior distribution.

The resultant posterior distribution will serve as a starting point for further trials within this area, whether as a key part of any information data packs provided to experts ahead of an elicitation meeting, or directly as the informed prior or hypotheses for further trials (5) (6).
A calibrated Bayesian hierarchical model (CBHM) described by Chu and Yuan (1) was planned to analyse the data, allowing data to be analysed by group and results from each group be used to enrich the data of the other groups. The calibration of the model allows strong information sharing when the treatment effect is similar among baskets, and shrinks that sharing towards 0 as the treatment effect becomes more heterogeneous.
Given the early termination of the study and the low recruitment in cohorts 1 and 3, the enrichment of groups with information from the other treatment groups will not be possible. Therefore, no CBHM will be performed for the main analysis and the information of the different cohorts will be combined, if applicable, only for safety analysis. The primary endpoint: 1-month† all-cause mortality rate will be studied by means of descriptive mortality rate analysis.

Primary Endpoint

The difference between treatment and control arms in all-cause mortality at 30 days was foreseen to be examined using a Bayesian comparison of proportions within the calibrated Bayesian hierarchical model (CBHM) framework described by Chu and Yuan (1).
As each basket completes, they would have been evaluated for efficacy, with information gained being used to update the analyses of successive baskets.

Due to the premature study closure no Bayesian specific outputs or sensitivity analyses will be generated

Secondary Endpoints/Other Endpoints

Frequency tables will be prepared for categorical variables, and continuous variables will be described by means of summary tables, which will include the median, mean, standard deviation, interquartile range, minimum, and maximum of each variable.
Frequentist methods will be calculated. Counts and percentages, with their corresponding exact confidence intervals, will be calculated for the binomial endpoints.
Time-to-event variables (e.g. key secondary endpoint) and their set time estimates will be defined as time from randomization to their corresponding event + 1 (see 8.3 section) and analysed according to the Kaplan-Meier method.
Key secondary endpoint, time to confirmed negativisation in SARS-CoV-2 antigen test or RT-PCR Ct > 30, will be analysed according to the Kaplan-Meier method.

<NOTE: Due to the premature study closure no complex specific outputs or sensitivity analyses will be generated>.

11.6.1 Primary Estimand

The primary estimand corresponding to the primary endpoint is defined as:

Treatment: Participants will be randomised to receive plitidepsin versus control in each group.

Population: Participants as defined through the inclusion and exclusion criteria, who have been randomised to the trial and who have taken at least 1 dose of study treatment (plitidepsin or control).

Variable:
–1-month all-cause mortality rate (Day 30 since randomisation).

Intercurrent events:

- The participant's data are collected and included in the analysis without regard for treatment discontinuation (treatment-policy strategy).
- In the event of the participant initiating another non-protocol therapy, 1-month all-cause mortality rate will be evaluated regardless of initiation of new non-protocol therapy (treatment-policy strategy).

Population level summary: the posterior probability associated for the odds ratio of 1-month all-cause mortality rate from a Bayesian logistic regression for each group comparison including point estimate and credible interval will be shown.

The cut-off for considering further clinical development of plitidepsin in each randomized group will be a posterior probability of superiority for the experimental arm equal to or greater than 65%.

<NOTE: Due to the premature study closure no Bayesian specific outputs will be generated and descriptive data will be shown>.

11.6.2 Key Secondary Estimand

The key secondary estimand corresponding to the key secondary endpoint is defined as:

Treatment: Participants will be randomised to receive plitidepsin versus control in each group.

Population: Participants as defined through the inclusion and exclusion criteria, who have been randomised to the trial and who have taken at least 1 dose of study treatment (plitidepsin or control).

Variable:
–Time to confirmed negativisation in SARS-CoV-2 antigen test or RT-PCR Ct > 30 calculated as date/time of survival event – first dose date/time of Investigational Product administration.

Intercurrent events:

- The participant's data are collected and included in the analysis without regard for treatment discontinuation (treatment-policy strategy).
- In the event of the participant initiating another non-protocol therapy, time to confirmed negativisation will be evaluated regardless of initiation of new non-protocol therapy (treatment-policy strategy).

Population level summary: the hazard ratio from a Cox regression for each group comparison including point estimate and confidence interval will be shown.

<NOTE: Due to the premature study closure no complex specific outputs will be generated and descriptive data will be shown>.

11.7 Safety Analyses

Safety analyses will be based on the As Treated Population. All safety parameters will be summarised, plotted and also listed by patient/events.

A treatment-emergent adverse event is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in intensity following exposure to the treatments.

Treatment-emergent Adverse Events: The verbatim terms used in the electronic case report form (eCRF) by investigators to identify TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded according to NCI CTCAE version 5.0. Treatment-emergent AEs will be summarised by MedDRA system organ class and preferred term by number of patients and by number of events. For each TEAE, the percentage of subjects who experience at least 1 occurrence of the TEAE will be summarised overall and by treatment group. The SAEs, AEs of special interest, and deaths will be listed including the study period (see Section 8.2) that they occur. All TEAEs resulting in discontinuation of study treatment will be listed and summarised by system organ class/preferred term.

AEs, SAEs, deaths, laboratory evaluations, and study drug discontinuations due to AEs will be tabulated in a descriptive way. Counts and percentages will be used for categorical variables, and summary tables will be used for continuous variables.

Any treatment-related adverse events (including Unknown relationship but potentially related), treatment-emergent adverse events of special interest, and SAES (including those with seriousness missing) that will measured daily until resolution or stabilisation to at least Grade 1, or to an acceptable level according to the investigator and the sponsor of his/her designated representative.

Clinical Laboratory Tests, see protocol sections 5.5.1/5.7/5.8/5.9 and appendix 8 to differentiate local or central. Laboratory data will be summarised by type of laboratory test. The worst toxicity grade will be tabulated. Parameters with predefined NCI CTCAE version 5.0 toxicity grades will be summarised. Change from baseline to the worst TEAE grade experienced by the subject during the study will be provided as shift tables.

- Haematology: haematocrit, red blood cells (RBC), differential WBC counts (including neutrophil and lymphocyte counts), platelet count and haemoglobin.
- Biochemistry: Liver function test [ALT, AP, AST, albumin, total bilirubin (direct bilirubin if total is abnormally elevated)], lactate dehydrogenase (LDH), glucose [fasting], sodium, potassium, calcium, BUN/urea, gamma glutamyl transferase (GGT), creatinine, calculated creatine clearance [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)], CPK, amylase, lipase, pro-calcitonin, ferritin, and CRP.
- Coagulation (D-Dimer).
- Urine analysis (semi-quantitative elemental tests for specific gravity, blood, pH, proteins, bilirubin, glucose, ketones, nitrites, and qualitative analysis of the sediment).

11.7.1 Adverse Event of Special Interest

The following AEs will be considered and monitored as AEs of special interest (AESIs): musculoskeletal disorders, CPK increases, and rhabdomyolysis; hypersensitivity reactions, cardiac events and transaminase elevations, thromboembolic events, and hepatobiliary disorders.

If at any time AST/ALT levels are greater than 3 x ULN (> 5 x ULN if pre-existent liver involvement at baseline by the underlying disease, with baseline ALT levels between 3-5 x ULN):

- Report as an AESI.
- The investigator should ensure that serum liver enzyme tests, serum bilirubin, and coagulation tests (INR or equivalent) are repeated two or three times weekly (local labs). Frequency of re-

testing can decrease to once a week or less if abnormalities stabilise or the trial drug has been discontinued and the subject is asymptomatic.

- The list of concomitant medications should be re-checked, and include nonprescription drugs, herbal and supplementary preparations, alcohol and recreational substances.
- Other reasons for liver injury should be ruled out, including co-infection with other virus, autoimmune or alcoholic hepatitis, non-alcoholic liver steato-hepatitis, biliary tract disease, progression of an underlying disease (e.g. liver metastasis), hypoxic/ischemic hepathopathy, or exposure to environmental agents.
- The investigator should consider additional tests to evaluate liver function or structure, as well as a consultation to specialists in liver diseases.

Treatment with plitidepsin must be discontinued in case of:

- ALT or AST > 8 x ULN;
- ALT or AST > 3 x ULN and either total bilirubin >2 x ULN or INR >1.5;
- ALT or AST > 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

11.7.2 IDMC safety report

IDMC requested specific outputs based on the publication (submitted): DMC reports in the 21st century. Towards better tools for decision-making, Vandemeulebroecke M., Baillie, M. Mirshani, A. and Lesaffre E.

Due to the premature study closure and suspension of the IDMC activity, no specific outputs or sensitivity analyses will be generated

11.8 Summary of Statistical Tests

All the main characteristics for estimands to fulfill study objectives will be defined as footnotes in each table following a similar structure than primary estimand definition. Below it can be found the endpoints to measure the variable definition and the analysis method to be used. Treatment attribute is maintained as 'participants will be randomised to receive plitidepsin versus control in each group' whereas applicable and sensitivity analyses according populations defined in 8.5 will be calculated. For intercurrent events, while applicable, a treatment-policy strategy as defined for the primary estimand will be followed.

Table 3 Summary of statistical tests

Endpoints	Analyses	Population
Efficacy primary endpoint		
1-month all-cause mortality rate.	-Frequencies	-FAS population
Key secondary endpoint		
Time to confirmed negativisation in SARS-CoV-2 antigen test or RT-PCR Ct > 30.	-Kaplan-Meier (unstratified)	-FAS population

Endpoints	Analyses	Population
Efficacy secondary endpoints		
Time to sustained end of COVID-related hospital care from the time of randomisation. Sustained discharge is defined as no subsequent admission within 30 days of initial end of hospital care [up to day 60 (±3)], related to either COVID-19 or COVID-19 therapy	-Kaplan-Meier (unstratified)	-FAS population
Time to sustained improvement (defined in Protocol Section 7.1.3) and resolution of selected COVID signs/symptoms (See Protocol Appendix 10 - COVID-19 signs/symptoms checklist).	-Kaplan-Meier (unstratified)	-FAS population
Distribution of patients according to their clinical status by the 11-category WHO Clinical Progression Scale, at Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3) (See Protocol Appendix 1 – 11-Point World Health Organization (WHO) Clinical Progression Scale).	-Frequencies	-FAS population
Percentage of patients requiring oxygen therapy on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Time to sustained discontinuation (i.e., at least 7 days) of oxygen supplementation.	-Kaplan-Meier (unstratified)	-FAS population
Safety secondary endpoints		
Treatment-emergent adverse events (TEAEs).	-Frequencies (severity grade by NCI-CTCAE v5)	-As treated population
TEAEs ≥ grade 3 according to the National Cancer Institute	-Frequencies	-As treated population

Endpoints	Analyses	Population
[NCI]-Common Terminology Criteria for AEs (CTCAE v.5.0).		
Adverse events of special interest (AESIs).	-Frequencies (severity grade by NCI-CTCAE v5)	-As treated population
Serious adverse events (SAEs).	-Frequencies (severity grade by NCI-CTCAE v5)	-As treated population
Drug related Serious Adverse Events (i.e., SARs).	-Frequencies (severity grade by NCI-CTCAE v5)	-As treated population
Adverse events leading to treatment discontinuation.	-Frequencies (severity grade by NCI-CTCAE v5)	-As treated population
Deaths (COVID-19-related/all).	-Frequencies	-As treated population
Change respect to baseline in individual study-defined laboratory parameters (See Protocol Section 5.7, 5.8 and 5.9 and Appendix 8 - Clinical Laboratory Analyses).	-Frequencies (severity grade by NCI-CTCAE v5)	-As treated population
Change respect to baseline in individual vital signs (See Protocol Section 5.7, 5.8 and 5.9).	-Frequencies	-As treated population
Other Secondary/Exploratory Endpoints		
Percentage of patients requiring advanced oxygen support on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2,) and 60 (±3).	-Frequencies	-FAS population
Time to intensification of respiratory support (WHO >5) (See Protocol Appendix 1 – 11-Point World Health Organization (WHO) Clinical Progression Scale).	-Kaplan-Meier (unstratified)	-FAS population
Total duration of advanced oxygen support.	-Summary statistics	-FAS population

Endpoints	Analyses	Population
Percentage of patients requiring high-flow oxygen on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Total duration of high-flow oxygen therapy per patient.	-Summary statistics	-FAS population
Percentage of patients requiring non-invasive mechanical ventilation on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Total duration of non-invasive mechanical ventilation per patient.	-Summary statistics	-FAS population
Percentage of patients requiring invasive mechanical ventilation or ECMO on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Total duration of invasive mechanical ventilation or ECMO per patient.	-Summary statistics	-FAS population
Percentage of patients requiring admission to ICU on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Total duration of intensive care unit (ICU) stay.	-Summary statistics	-FAS population
Time to onset of additional (i.e., not present at baseline) immune-modulating drugs.	-Kaplan-Meier (unstratified)	-FAS population
Percentage of patients receiving immune-modulating drugs on Days 1, 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Time to onset of additional (i.e., not present at baseline) antiviral drugs.	-Kaplan-Meier (unstratified)	-FAS population

Endpoints	Analyses	Population
Percentage of patients receiving subsequent antiviral drugs (i.e., not present at baseline) on Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Percentage of patients with a new infection by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Cumulative mortality (all-cause and related to COVID-19) by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Percentage of patients in each study group who require subsequent admission within 30 days of initial end of hospital care [up to day 60(±3)], related to either COVID-19 or COVID-19 therapy.	-Frequencies	-FAS population
Change respect to Day 1 in the viral load of SARS-CoV-2, measured by RT-PCR, by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3), in each study group.	-Summary statistics	-FAS population
Percentage of patients in each study group with undetectable viral load, by Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3).	-Frequencies	-FAS population
Time to either undetectable viral load of SARS-CoV-2 or > 2 logs reduction respect to Day 1.	-Kaplan-Meier (unstratified)	-FAS population
Change respect to baseline in inflammatory biomarkers (C-reactive protein [CRP], procalcitonin, lactate dehydrogenase [LDH], ferritin, neutrophil-to-lymphocyte ratio, and multiplex cytokines assay,	-Summary statistics	-FAS population

Endpoints	Analyses	Population
by Day 4 (±1), 8 (±1), 15 (±1) and 30 (±2) and 60 (±3).		
Change respect to baseline in individual serological assessments against SARS-CoV-2, by Days 30 (±2), and 60 (±3).	-Summary statistics	-FAS population
Change respect to baseline in individual T-cell response against SARS-CoV-2 by Days 30 (±2), and 60 (±3).	-Summary statistics	-FAS population
Change respect to baseline to Days 15 (±1), and 30 (±2) in chest X-ray findings (Brixia score, centrally assessed) (Protocol Appendix 9 – Brixia Score).	-Summary statistics	-FAS population
Percentage of patients requiring modification of the therapy (drugs, dose or schedule) for the underlying disease.	-Frequencies	-FAS population
Time in which pre-scheduled therapies for the control of the underlying disease were not able to be administered.	-Kaplan-Meier (unstratified)	-FAS population
Risk for mortality / clinical deterioration according to individual clinical characteristics and laboratory observations present at baseline, scores of validated scales (e.g., ISARIC-4C), as well as features related to COVID-19 [including SARS-CoV-2 variant (if available), vaccination status, duration of the infection, and inflammation-related parameters [neutrophil-to-lymphocyte ratio (NLR), protein C reactive, interleukine-6 (IL-6) and lymphocytes], the underlying disease, and other co-morbidities.	-Frequencies	-FAS population

Endpoints	Analyses	Population

<NOTE: Due to the premature study closure no Bayesian or specific outputs or sensitivity analyses will be generated>.

11.9 Vital signs, Physical Examinations, ECGs, Chest Imaging and Other Observations Related to Safety

Vital signs, physical examination, ECGs, chest imaging and respiratory assessments data including oxygen therapy supplementation status and their changes from baseline will be summarized by visit using standard descriptive statistics for the as treated population.

11.10 Pooled and Subgroup Analyses

Exploratory pooled analyses will be performed for safety endpoints.

<NOTE: Due to the premature study closure no specific outputs will be generated for subgroup analysis>.

11.11 Pharmacokinetic and Pharmacodynamics Analyses

These analyses will be detailed and reported in separate documents.

12.0 References

1. Y. C, Y. Y. A Bayesian basket trial design using a calibrated Bayesian hierarchical model. Clinical trials (London, England). 2018;15(2).

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5. V. HL, Whitehead J, Eleftheriou D, Tudur-Smith C, Jones R, Jayne D, et al. Elicitation of expert prior opinion: application to the MYPAN trial in childhood polyarteritis nodosa. PloS one. 2015;10(3):e0120981.

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13.0 Statistical Software

JAGS program running in R version 4.2.1 (3) on Microsoft Windows 10 for simulations and sample size derivation for randomised groups (1-3) and https://www2.ccrb.cuhk.edu.hk/stat/phase2/Fleming.htm for Non-controlled group 4.

SAS® v.9.4 or higher will be used for statistical analysis outputs.

14.0 Glossary of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ATC	Anatomical Therapeutic Chemical
BSC	Best Standard Care
CBHM	Calibrated Bayesian Hierarchical Model
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organisation
CRP	C- reactive Protein
CRF	Case Report Form
eCRF	Electronic Case Report Form
ECMO	Extracorporeal Membrane Oxygenation
EOS	End of Study
FAS	Full Analysis Set
FPI	First Patient In
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
h	Hour
ICF	Informed Consent Form
ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IL-6	Interleukine-6
IMP	Investigational Medicinal Product
IRR	Infusion-related (i.e., plitidepsin-related) Reactions
IV	Intravenous
JAGS	Just Another Gibbs Sampler
LDH	Lactate Dehydrogenase
LPLV	Last Patient Last Visit
MCMC	Markov-chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NLR	Neutrophil-to-Lymphocyte Ratio
PK/PD	Pharmacokinetic(s)/Pharmacodynamic(s)
PP	Per Protocol
Q1-Q3	Interquartile Range
RBC	Red Blood Cells
RT-PCR	Real Time Polymerase Chain Reaction
SAE	Serious Adverse Event

SAR	Drug related Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
STD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
vs	versus
WHO	World Health Organization