APLICOV-PC (APL-D-002-20)

Multicenter, randomized, parallel and proof of concept study to evaluate the safety profile of three doses of Plitidepsin in patients with COVID-19 requiring hospitalization

STATISTICAL ANALYSIS PLAN

Version: 1.0
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-Confidential-

CONTENTS

1 INTRODUCTION

This statistical analysis plan describes the protocol-defined final analysis that will be performed in the APLICOV-PC study (APL-D-002-20).

Given the characteristics of the study, continuous safety analyses up to 12 days after the last administration of plitidepsin of each patient evaluable for safety in each of the arms of each group of 9 patients are planned to be performed. These analyses will be performed for every 3 patients included in each arm of each cohort, before continuing with the inclusion of more patients in the study. After the recruitment of the 27 initially planned patients, an additional 18 patients will be included (6 at each dose level) to expand the collection of safety information of the different doses and to increase the efficacy data.

This SAP version applies to the final statistical analysis that will be the basis of the clinical study report and it will be made on the total population of 45 patients. These analyses will be descriptive and the data will be presented by treatment arm.

Abbreviations:

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BPM	Breaths per minute or Beats per minute
CPK	Creatine Phosphokinase
DBP	Diastolic blood pressure
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
GGT	Gamma-glutamyltransferase
ICU	Intensive care unit
IL-6	Interleukin 6
LDH	Lactate dehydrogenase
SAE	Serious Adverse Event
SBP	Systolic blood pressure

2 SYNOPSIS

2.1 Title of the study

“Multicenter, randomized, parallel, open-label study, to evaluate the safety profile of three doses of plitidepsin in patients with COVID-19 requiring hospital admission."

2.2 Code of the study

APLICOV-PC (APL-D-002-20).

2.3 Sponsor

Pharma Mar, S.A

2.4 Design

Randomized, multicenter clinical trial with three treatment arms.

Three cohorts of 9 patients will be included in the study. Each 9 patient cohort will include 3 arms (A, B and C) with different dose levels with 3 patients in each arm, up to a maximum of 27 evaluable patients for safety. An additional 18 patients will be included (6 at each dose level) to expand the collection of safety information of the different doses and to increase the efficacy data.

The established dose levels are the following:

- Arm A) 1.5 mg of plitidepsin, 1.5 hour infusion, once a day for 3 consecutive days.
- Arm B) 2.0 mg of plitidepsin, 1.5 hour infusion, once a day for 3 consecutive days.
- Arm C) 2.5 mg of plitidepsin, 1.5 hour infusion, once a day for 3 consecutive days.

Arm	**Dose Level**	**Daily dose (mg)**	**Total dose (mg)**
Arm A	1	1.5 mg x 3 days	4.5 mg
Arm B	2	2.0 mg x 3 days	6.0 mg
Arm C	3	2.5 mg x 3 days	7.5 mg

Enrollment will be sequential in each of the three arms. The first cohort of 3 patients in arms B and C (2.0 mg and 2.5 mg) will not be opened until the data for the first 3 patients at the prior lower dose level (arms A or B) have been analyzed, without any unacceptable toxicity, taking into account the three included patients in each arm will be followed for 12 days from the end of the treatment (day +15 after the start of treatment).

When patients could be enrolled in more than one dose level (arm), patients will be randomized by 1:1 or 1:1:1 ratio, as appropriate.

The following criteria have been established to continue the inclusion of patients in the different arms:

- In case of 0-1 out of the first three treated patients at dose of 1.5 mg x 3 days has grade 3 or higher adverse event in the twelve days after the administration of the last dose, three additional patients will be recruited in the 1.5 mg arm and the enrollment of the first three patients in the 2.0 mg arm will be opened. Enrollment in the 2.5 mg arm will be opened after only 0-1 out of the three patients in the first cohort in the 2.0 mg arm has grade 3 or higher toxicity within twelve days follow-up after the last 2.0 mg dose.
- If in any of the arms, 2 or more patients have a grade 3 or higher adverse event, the sponsor will interrupt the enrollment of new patients and will review with the Spanish Agency for Medicines and Health Products the convenience of continuing the enrollment in that arm in other arm with a

higher dose.

Intra-patient dose change/increase is not allowed.

Once the 27 patients (9 in each dose level) will be included, an extension period to include 18 additional patients (6 in each plitidepsin dose level) to expand the collection of safety information for the different doses and to collect efficacy data will be performed. After this extension period, data will be available from 15 patients at each plitidepsin dose level. During the extension period, patients will be randomized by 1:1:1 ratio.

2.5 Study Objectives

Primary objective:

- Determine the safety and toxicological profile of plitidepsin at each dose level administered according to the proposed administration schedule in patients admitted for COVID-19.

Secondary objectives:

- Evaluate the efficacy of plitidepsin in COVID-19 patients at proposed dose levels by:
  - Change in SARS-CoV-2 viral load from baseline
  - Time to negative detection of SARS-CoV-2 by PCR.
  - Cumulative incidence of disease severity. It will be evaluated by:
    - Deaths
    - Need for invasive mechanical ventilation and/or ICU admission
    - Need for non-invasive mechanical ventilation
    - Need for oxygen therapy
- Selection of the recommended dose levels of plitidepsin for conducting a phase II/III efficacy study.

2.6 Endpoints

Primary endpoints:

To set the safety and toxicological profile of plitidepsin at each dose level administered in patients admitted for COVID-19, the following variables will be analyzed:

- Occurrence frequency of the following grade ≥ 3 adverse events according to the NCI-CTCAE criteria v5.0 at 3, 7, 15 and 31 days:
  - Hematological
    - Neutropenia
    - Thrombocytopenia
    - Anemia
    - Lymphopenia
  - Non hematological
    - CPK increase
    - ALT and/or AST increase
    - Total bilirubin increase or direct bilirubin

    - Neurotoxicity
    - QT-QTc interval prolongation
  - Other grade ≥ 3 adverse events

- Percentage of patients with uncompleted treatment and the reasons.

- Percentage of patients with AEs and SAEs at days 3, 7, 15 and 31.

- Changes from baseline (day -1 or day 1 before administration of study medication) in hematological and non-hematological parameters on days 3, 7, 15, 31.

- Percentage of patients with ECG abnormalities at days 2, 3, 4, 5, 6, 7, 15 and 31.

Secondary endpoints:

- Change from baseline in SARS-CoV-2 viral load (day -1 or day 1 before administration of study medication) measured at 3, 4, 7, 15, and 31 days.

- Time to negative detection of SARS-CoV-2 by PCR obtained in nasopharyngeal swab or sample from the lower respiratory tract compared to baseline (day -2 or -1 or day 1 before administration of study medication).

- Deaths at 7, 15 and 31 days.

- Percentage of patients that need for invasive mechanical ventilation at 7, 15, and 31 days.

- Percentage of patients that need for non-invasive mechanical ventilation at 7, 15, and 31 days.

- Percentage of patients that need for oxygen therapy at 7, 15 y 31 days.

- The recommended dose level will be selected after the evaluation of the safety and efficacy data obtained in this study between the sponsor and the Spanish Agency for Medicines and Health Products.

2.7 Study population

Three cohorts of 9 patients each of the three dose levels will be included in the study. The enrollment will be sequential in blocks of 3 patients in each dose level until a maximum of 27 patients are included. Once the 27 patients (9 in each dose level) will be included, an extension period to include 18 additional patients (6 in each plitidepsin dose level) for expand the collection of safety information for the different doses and to collect efficacy data will be performed.

2.8 Inclusion criteria

1. Patient who agrees to participate in the study by signing the informed consent.
2. Men and women (not pregnant) with age ≥18 years.
3. PCR-confirmed COVID-19 infection obtained from nasopharyngeal swab or sample from the lower respiratory tract.
4. Patients requiring hospitalization for COVID-19.

5. Symptoms onset within 10 days prior to study enrollment.

6. Men and women of childbearing potential must agree to use highly effective contraception (diaphragm and spermicidal or male condom and spermicide, oral contraceptive combined with a second method of contraceptive implant, injectable contraceptive, permanent intrauterine device, sexual abstinence or vasectomy) during their participation in the study and for 6 months following the last plitidepsin administration.

7. Women of childbearing potential participating in the study must have a negative pregnancy test at the time of inclusion.

2.9 Exclusion criteria

1. Patients participating in any other clinical trial for COVID-19 infection.
2. Patients receiving antivirals or interleukin 6-receptor treatment-inhibitors and immunomodulator drugs for COVID-19.
3. Patients receiving chloroquine and derivatives treatment.
4. Multiorgan failure evidence.
5. Patients requiring support with mechanical ventilation (invasive or non-invasive) at the time of inclusion.
6. D-dimer > 4 x ULN .
7. Hb < 9 g/dL.
8. Neutrophils < 1000/mm^3.
9. Platelets< 100.000/mm^3.
10. Lymphopenia < 800/µL.
11. AST / ALT > 3 x ULN.
12. Bilirubin > 1 x ULN.
13. CPK > 2.5 x ULN.
14. Creatinine clearance < 30ml/min.
15. Troponin increased > 1.5 xULN.
16. Clinically relevant heart disease (NYHA >2).
17. Clinically relevant arrhythmia or previous history / presence of prolonged QT-QTc ≥ 450 ms.
18. Any kind of pre-existing neuropathies grade ≥ 2.
19. Hypersensitivity to the active substance or any of its excipients (macrogolglycerol ricinoleate and ethanol).
20. Patients requiring or being treated with strong CYP3A4 inhibitors and inducers.
21. Patients who for any reason should not be included in the study as assessed by the research team.

3 GENERAL PRINCIPLES

Planned analyses in this document will be carried out once the database is declared cleaned, closed and approved by Pharma Mar according to the premises described in the Data Management Plan version 2.0 approved on 09 June 2020.

Statistical analyses will be performed using SAS software version 9.4 and R. The results of the analyses will be presented in editable format (i.e rtf).

The data will be provided with one decimal place in general. In those cases where greater precision is required, as many decimal places as necessary will be provided.

Before to perform the analyses, the following activities will be performed:

Codification/revision and approval of the following terms:

- Adverse events /procedures according to MedDRA dictionary (latest version available).
- Medication according to the WhoDrug dictionary (latest version available).
- Reconciliation of serious adverse events in the study between the clinical database and the Pharmacovigilance database and resolution of all discrepancies.

Analysis will be done separately for each arm and the total population.

Continuous variables will be presented through the mean, median, standard deviation, range, Q1, Q3 and categorical variables will be presented through the distribution of frequencies and percentages; missing values will not be taken into account in the percentage calculation, percentages with valid data will be presented.

3.1 Analyses to perform by cohort in the interim analysis

3.1.1 First analysis: First group (3 patients)

The first group of 3 patients will be from treatment arm A. After patients have completed 12 days from the last plitidepsin administration, a safety analysis will be performed.

3.1.2 Second analysis: second group (6 patients)

If the previous analysis concludes that the study can continue, a second group of 6 patients will be added to the 3 previous patients who have already finished the treatment, who will be randomized 1:1 in arms A and B. When these new patients finish the 12 days follow-up after the last plitidepsin administration, a second analysis will be done. In this analysis, the new group of patients and the total number of patients in the study will be studied. An analysis of the 6 new patients and another of the 9 total patients included in the study will be performed, 3 patients from the first group and 6 patients from the second group, having 6 patients in arm A and 3 patients in arm B.

3.1.3 Third analysis: Third group (9 patients)

If the analysis of the second group of patients and the total of 9 study patients conclude that the study can be continued, 9 new patients will be recruited, who will be randomized 1:1:1 among arms A, B and C, if the previous analysis does not involve the closure of arm B. When these patients finish the 12 days follow-up period from the last plitidepsin administration, the new patients will be analyses and an aggregate analysis with all the study patients will be performed.

3.1.4 Fourth analysis: Fourth group (6 patients)

If the analysis of the third group of patients and the total of 18 study patients conclude that the study can be continued, 9 new patients will be recruited, who will be randomized 1:1:1 among arms A, B and C, if the previous analysis does not

involve the closure of arm B or C. When these patients finish the 12 days follow-up period from the last plitidepsin administration, the new patients will be analyses and an aggregate analysis with all the study patients will be performed.

3.1.5 Fifth analysis: Fifth group (3 patients)

If the last analysis concludes that the study can be continued, 3 new patients will be recruited, who will be included in the arm C, if the previous analysis does not involve the closure of this arm. When these patients finish the 12 days follow-up period from the last plitidepsin administration, the new patients will be analyses and an aggregate analysis with all the study patients will be performed.

4 STUDY POPULATION

4.1 Definition of the study population to be analyzed

The safety population will include all enrolled/randomized patients who received at least one dose (full or not) of plitidepsin.

The efficacy population will included all patients who have received all three doses of treatment and have completed a follow-up period of at least 2 weeks. Those patients who did not complete the treatment period due to the unfavorable evolution of the disease will be also included in for the efficacy population.

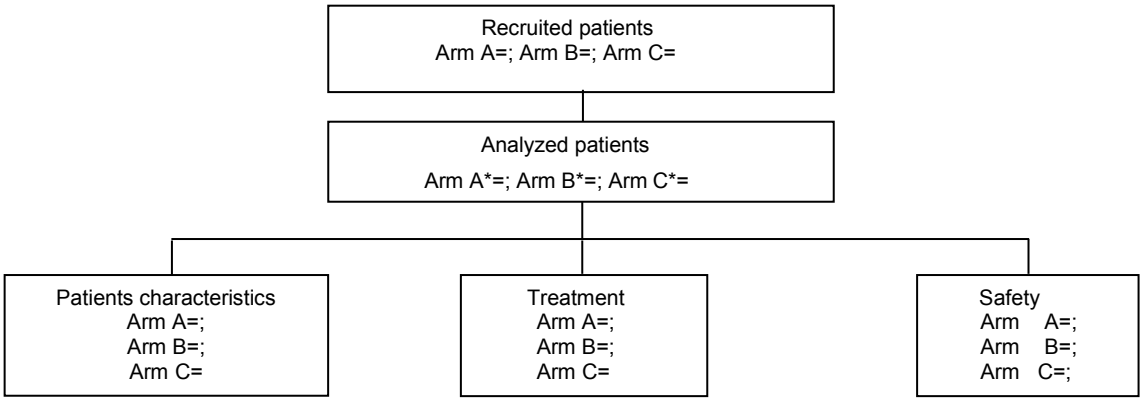
4.2 Patients disposition

The number and percentage of patients per center will be provided and the recruitment period will also be indicated.

Patient's disposition in safety population will be described with the following diagram.

Patients disposition are described in the following diagram and additionally it will be specified which patients will be analyzed in the safety and efficacy population:

Figure 1: Patient's disposition



* Discrepancies between the number of patients analyzed and the number of patients recruited will be described (screening failures).

All analysis will be performed separately for each arm and a total column will be added.

4.3 End of treatment

The number and percentage of patients who completed or not the treatment will be provided. In those who finished treatment early, the causes of termination will be described.

All the analyses will be performed separately for each arm and a total column may be added if needed.

4.4 End of study

The number and percentage of patients who completed or not the study will be provided. For those patients who finished study early, the causes of termination will be described.

All analysis will be performed separately for each arm and a total column may be added if needed.

4.5 Deaths

The number and percentage of patients who died during the study and the reasons will be provided. Patients who have died due to an adverse event will be described in more detail, indicating all the variables related to the AEs registered in the application.

All the analyses will be performed separately for each arm and a total column may be added if needed.

4.6 Missing data

Missing data imputation is not foreseen.

5 PATIENTS DESCRIPTION

5.1 Demographic data description. General considerations.

The characteristics of the patients in the safety population will be described and the not available information will be detailed. Continuous variables will be presented through the mean, median, standard deviation, range, Q1, Q3 and categorical variables will be presented through the distribution of frequencies and percentages; not available values will not be taken into account in the percentage calculation, only valid percentages will be presented. The analysis will be carried out on the full safety population and all results will be provided by treatment arm. Aggregated results as well as patient listings will be provided.

5.2 Patients characteristics

In this section the following variables will be described:

a) Demographic data:
   - Age (years) (continuous).
   - Age (<65 years; ≥ 65 years).
   - Gender (Male/Female).
   - Ethnic group (Arabic; White; Latin; Asian; Black; Other).

b) Clinical data: Patient status:
   - FDA classification: Mild, Moderate and Severe.
   - Six-point ordinal scale: On day 1 (first administration day), patients will be classified according to the following six-point ordinal scale:

1. Discharge (Alive)
2. Hospital admission, not requiring supplemental oxygen.
3. Hospital admission, requiring supplemental oxygen.
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation.
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation.
6. Death.

c) Clinical data: Signs and symptoms on admission:
   - Time from the beginning of the first symptom: The time from the beginning of the first symptom is defined as the difference, in days, between the date of the first dose of plitidepsin administration and the date of the beginning of the first symptom.
   - Time from the beginning of the first symptom to hospital admission (days).
   - Fever history (Yes/No).
   - Dehydration (Yes/No).
   - Cough (Yes/No). In affirmative case, describe:
   - Sputum production (Yes/No). In affirmative case, describe:
   - Bloody sputum/ Hemoptysis (Yes/No).
   - Runny nose (rhinorrhea) (Yes/No).
   - Earache (Yes/No).
   - Crackles (Yes/No).
   - Thoracic pain (Yes/No).
   - Muscular pain (myalgia) (Yes/No).
   - Joint pain (arthralgia) (Yes/No).
   - Fatigue / malaise (Yes/No).
   - Short of breath (dyspnea) (Yes/No).
   - Intercostal retraction (Yes/No).
   - Headache (Yes/No).
   - Altered state of consciousness / confusion (Yes/No).
   - Convulsion (Yes/No).
   - Abdominal pain (Yes/No).
   - Vomiting / nausea (Yes/No).
   - Diarrhea (Yes/No).
   - Conjunctivitis (Yes/No).
   - Rash (Yes/No).
   - Skin ulcer (Yes/No).
   - Lymphadenopathy (Yes/No).
   - Throat pain (Yes/No).
   - Bleeding (hemorrhage) (Yes/No). If so, the description of the bleeding locations will be detailed.

d) Clinical data: Comorbidities:
   - Chronic cardiac pathologies including congenital cardiac pathologies (does not include hypertension) (Yes/No).
   - Arterial hypertension (Yes/No).
   - Chronic lung disease (does not include asthma) (Yes/No).
   - Asthma (medical diagnosis) (Yes/No).

- Diabetes with complications (Yes/No).
- Diabetes without complications (Yes/No).
- Chronic kidney disease (Yes/No).
- Rheumatic disorder (Yes/No).
- Moderate or severe liver disease (Yes / No).
- Mild liver disease (Yes/No).
- Dementia (Yes/No).
- Malnutrition (Yes/No).
- Chronic neurological disorder (Yes / No).
- Smoker (Yes/No).
- Malignant neoplasm (Yes/No).
- Chronic hematological disease (Yes / No).
- AIDS / HIV (Yes / No).
- Obesity (define by medical staff) (Yes/No).
- Other risk factors (Yes / No). If so, the description of the specified factors will be detailed.

e) Vital signs at baseline
   - SBP (mmHg) (continuous).
   - DBP (mmHg) (continuous).
   - Heart rate (l.p.m.) (continuous).
   - Respiratory rate (r.p.m.) (continuous).
   - Temperature (ºC) (continuous).
   - Saturation O_2 (%) (continuous).
   - Saturation (Room air/Oxygen therapy/Not available). In the case of oxygen therapy, the following will be described:
     - Oxygen therapy type (Nasal glasses; Simple mask; Venturi mask; Reservoir mask; Other). In case of other a detailed listing will be provided.
     - Flow (L/min) (continuous).
     - FiO_2 (%) (continuous).
     - PaO_2 (mmHg) (continuous)
     - PaO_2/FiO_2 o SaO_2/FiO_2 (continuous).
   - Chest X-ray (Yes/No). if so, the following will be described:
     - X-ray result (Normal/Abnormal). In case of abnormality, the abnormality will be detailed (Unilateral Pneumonia / Bilateral Pneumonia / Other). In case of other abnormality, the description of the abnormalities will be provided.
   - Electrocardiogram (Yes / No). If so, it will be described:
     - Result (Normal / Abnormal: Not clinically significant or Abnormal: clinically significant). In case of abnormality, the description of the abnormalities will be provided. (QT interval prolongation / PR interval prolongation / other alteration). In case of other alteration, the description of the other alteration will be provided.

f) Viral load (log copies / mL)

g) Summary of Demographic and Other Baseline Characteristics
   - Age, median (range) years

- Gender, % male
- Median (range) time from symptom onset to first plitidepsin administration, days
- Number of comorbidities, n (%) (none, one, two or more)
- Comorbidities, n (%) (Cardiac disease, Kidney disease, Liver disease, Lung disease (COPD), Asthma, Diabetes, Hypertension, Obesity)
- Clinical status at randomization, n (%)
- Vital signs, median (range) (Body temperature, ºC, Systolic blood pressure, mmHg,

  Diastolic blood pressure, mmHg, Heart rate, bpm, Respiratory rate, bpm, SpO2

  B, %, On oxygen at baseline, n (%))
- Laboratory parameters, median (range) (WBC, x109/L, Platelet count, x109/L, Lymphocytes, x109/L, Serum creatinine, µmol/L, ALT x ULN, AST x ULN, LDH x ULN, CPK x ULN, GGT x ULN, C-reactive protein, Ferritin, D-dimer)
- log10 copies/mL viral load, median (range)

6 TREATMENT DESCRIPTION

6.1 Administered treatment

The analysis of treatment administration will be carried out on the safety population and by treatment arm. The following variables will be analyzed:

- Days of treatment with plitidepsin (categorical).
- Total administered dose (continuous).
- Relative dose intensity (continuous). It will be calculated as the proportion between the total dose administered and the theoretical dose expected per protocol.

The variables will be analyzed on each of the treatment days (days 1 to 3): Administered treatment (Yes / No). If not, the reasons for non-administration will be described. If so, the variables will be described:

- Administered treatment dose (mg/day) (continuous).
- Treatment administration interrupted (Yes/No). If so, the reasons for interruption will be described.
- Pre-medication (Yes/No). If so, the description of the coded active substances (ATC) and grouped by type (antiemetic, gastric protector, antihistamine and corticosteroids) will be provided.

7 SAFETY EVALUATION

The safety analysis will be performed on the safety population defined in section 4.1. They will be presented by treatment arm as well as by treatment arm based on age groups (<65 years; ≥ 65 years) and the total population.

7.1 Safety evaluation. General considerations

Adverse events will be coded by using MedDRA (latest version available) and will be presented grouped by system (SOC) and preferred term (PT). The associated grades with each of the adverse events will be evaluated using the NCI-CTCAE V5.0 toxicity criteria.

To obtain the adverse events per patient, the maximum grade will be considered for each of the events collected for each patient. If the relationship between an adverse event and the study drug cannot be ruled out, it will be considered to be related for the analysis.

The analysis will be presented on days 3, 7, 15 and 31 after the start of study treatment:

The following results will be provided:

- Number and percentage of patients presenting the following adverse events with ≥ 1 grade change in:
  - Hematological parameters:
    - Neutropenia
    - Thrombocytopenia
    - Anemia
    - Lymphopenia
  - Non-hematological parameters:
    - CPK increase
    - AST increase
    - ALT increase
    - Total increase, or direct bilirubin
    - Neurotoxicity
    - QT-QTc interval prolongation
- Number and percentage of patients unable to complete treatment

- The number and percentage of patients with some AE or SAE will be presented:
  - From Day 1 to day 3
  - From Day 1 to day 7
  - From Day 1 to day 15
  - From Day 1 to day 31

- The number and percentage of patients with some SAE will be presented:
  - From Day 1 to day 3
  - From Day 1 to day 7
  - From Day 1 to day 15
  - From Day 1 to day 31

- The number and percentage of patients with some Grade ≥ 3 Adverse Events, Regardless of Relationship will be presented.
  - From Day 1 to day 3

- From Day 1 to day 7
- From Day 1 to day 15
- From Day 1 to day 31

- Patients with ≥ 1 grade change from baseline in hematologic parameters, from Day 1 to.
  - From Day 1 to day 3
  - From Day 1 to day 7
  - From Day 1 to day 15
  - From Day 1 to day 31

- Patients with ≥ 1 grade change from baseline in non-hematologic parameters, from Day 1 to
  - From Day 1 to day 3
  - From Day 1 to day 7
  - From Day 1 to day 15
  - From Day 1 to day 31

- The number and percentage of patients with some Treatment-Related Adverse Events will be presented.

- The number and percentage of Treatment-Related Adverse Events will be presented.

- The number and percentage of Adverse Events, Regardless of Relationship, by grade will be presented.

- The number and percentage of patients with some grade ≥3 Adverse Events, Regardless of Relationship will be presented.

- The number and percentage of grade ≥3 Adverse Events, Regardless of Relationship will be presented.

- The number and percentage of patients with some Treatment-Related Adverse Events, by grade, (treatment dose and Pre/Post relevant amendment nº9 (13AUG2020) and relevant amendment nº12 (11SEP2020)) will be presented.

- The number and percentage of patients with some Adverse Events, Regardless of Relationship, by grade, (treatment dose and Pre/Post relevant amendment nº9 (13AUG2020) and relevant amendment nº12 11SEP2020) will be presented.
- A detailed listing of patients with all adverse events related or not with plitidepsin indicating serious (yes / no), relation and grade will be provided.
- A detailed listing of patients with all the related adverse events with plitidepsin indicating serious (yes / no), relation and grade will be provided.
- A detailed listing of patient with all the non-related adverse events with plitidepsin indicating serious (yes / no), relation and grade will be provided.
- A detailed listing of patients who have died from a SAE will be provided.
- A detailed listing of patients who have suffered an adverse event that have caused treatment withdrawn or interruption will be provided.

7.2 Laboratory test evolution

For the analysis of the laboratory tests evolution, the percentage of change in each visit will be calculated with respect to the baseline view. The analysis will be performed on the safety population by treatment arm as well as by treatment arm based on age groups (<65 years; ≥ 65 years) and for the total of the population.

A listing of patients and the values of the laboratory parameters (hematology, coagulation and biochemistry) at baseline, and day 3, 7, 15 and 31 visits will be provided and those associated with an AE of any grade regardless of the relationship with plitidepsin will be highlighted.

The values of the parameters will be provided as well as the percentage change versus baseline, indicating the date and the units. Parameters will be standardized to equivalent units prior to data analysis.

Baseline value will be considered the last available value before or on the same day of the first drug administration.

7.3 Other safety evaluation

The analysis will be performed on the safety population by treatment arm as well as by treatment arm based on age groups (<65 years; ≥ 65 years).The following variables are described at baseline and on days 1, 2, 3, 4, 5, 6, 7, 15 and 31 of study treatment:

- Number and percentage of patients with alterations in the chest X-ray and the indicated anomalies will be described. The following variables will be described: no change, improvement, worsening.

- Evolution of the chest X-ray result per patient.
    - N (%) of patients with improvement in radiography on days 7, 15 and 31 after the first dose of plitidepsin
    - N (%) of patients with worsening in radiography on days 7, 15 and 31 after the first dose of plitidepsin
    - N (%) of patients with no changes in radiography on days 7, 15 and 31 after the first dose of plitidepsin

- Number and percentage of patients with ECG alterations and the detected alterations will be described.
- A list with the evolution of SaO2 in each of the controls carried out on the patients will be provided, indicating the type of saturation (air in the room / oxygen therapy / not available).
- Change in Vital Signs (median and range) from Baseline through Day 31. Calculated using the mean value when there were more than one assessment per day will be used for blood pressure measurements. Worst value per patient, per day, will be used for the rest of measurements.
    - Blood pressure, diastolic (mm Hg)
    - Blood pressure, systolic (mm Hg)
    - Heart rate (beats per minute)
    - Respiratory rate (breaths per minute)
    - pSO2 by pulse oximetry (%) (Room-air)

7.4 Concomitant medication

- Description of the concomitant medication: number of patients and percentage of some concomitant medication will be presented by dose and ATC levels.

The following variables will be analyzed per visit:

- Requirement of another specific treatment for COVID-19 (Yes; No).
- Support treatment requirement (Yes; No). For those patients who have received supportive treatment, the treatment and description in the database (discrete) and the treatment scheme taking into account the active principle of the medication (discrete) will be analyzed. The number and percentage of patients that require each of the schemes will be indicated and a detailed list of patients will be provided.
- Duration of corticosteroids treatment.
- Duration of antibiotic treatment

8 EFFICACY EVALUATION

The efficacy analysis will be performed on the efficacy population. Results will be presented separately for treatment arm and for the main endpoints, by age (<65 or ≥65 years old) and by FDA classification will be performed too.

8.1 Efficacy evaluation

The following tests will be performed to evaluate the efficacy of the treatment:

a) Viral load evolution:

For the analysis of the evolution of the viral load, the number and percentage of patients from who a sample has been collected will be indicated to determine the viral load at baseline and at visit 4, 7, 15 and 31 describing the results in those patients (number of RNA copies detected and log of the number of copies). The result will be given to three decimal places.

The graphs of the evolution of the viral load (mean and median) of the patients from the baseline to the last visit will be presented. These graphs will be shown by separate for each dose level, by FDA baseline classification and Oxygen support or not on day 1.

In addition, the following variables will be analyzed:

- The number and percentage of patients who viral load result is maintained, decreased or increased with respect to the previous visit on days 4, 7, 15 and 31 will be presented.
- Negative detection (global and by dose level):
- The number and percentage of patients with negative or undetectable viral load on days 4,7,15 and 31.
- The number and percentage of patients with negative or undetectable viral load on days 4,7,15 and 31 in the subgroups of low, medium and high initial viral load.
- Time to negative detection (viral load 0 or undetectable) in overall patients from date of PCR at baseline.
- Time to negative detection (viral load 0 or undetectable) based on baseline viral load (high (>7 copies/mL) / medium [4-7 copies/mL] / low (<4 copies/mL)) and other baseline characteristics (sex, age, race, ...) will be explored.
- Time to negative detection based on corticosteroid treatment (<10 days vs > 10 days)
- Viral load (high, medium, low) will be correlated with study outcome variables such as need for oxygen therapy, admission to ICU (Yes / No), NIMV, IMV, days of hospitalization, death (Yes / No).

- Determine the relationship between the number of days with symptoms and having a higher or lower viral load.
- Determine the relationship between viral load and the baseline situation of the patient, mild-moderate-severe, oxygen need / no need.
- The relationship between viral load and different inflammatory parameters (LDH, ferritin, C-reactive protein, D-dimer and lymphocytes) will be graphically analyzed.
- The mean change in viral load log 10 RNA copies/mL from baseline to day 4, 7, 31 will be analyzed in:
    - All patients
    - Moderate and Mild Patients following the FDA Classification
    - Moderate patients following the FDA Classification

b) COVID-19 evolution by PCR:

For the analysis of COVID-19 evolution by PCR, the number and percentage of patients who have taken the PCR test will be indicated at the baseline and at visit 4, 7, 15 and 31 describing the results (positive / negative) in those patients.

A list of PCR evolution of the patients from baseline to the last visit will be presented.

c) Time to negative detection of COVID-19 detection by PCR:

The time to negative detection of the detection of COVID-19 by PCR is defined as the time, in days, from the date of baseline PCR to the first PCR date with a negative result and does not have a positive result in the following PCR or having a negative result in the last PCR date (Day 31).

The following analyses will be presented.

The time to negative detection will be analyzed by the Kaplan-Meier method and the median and the 95% confidence interval will be provided.

- The number and percentage of patients with qualitative PCR at 4, 7, 15 and 31 days
- A descriptive table will be provided in which both variables are related to each of the variables indicated below:
    - Chronic lung disease (excluding asthma) (Yes; No).
    - Oxygen therapy on day 1 (Yes; No).
    - Plitidepsin dose
    - Days from symptoms until 1st dose of plitidepsin
    - Baseline severity of the disease
    - Age
    - Sex
    - Use of corticosteroids
    - Race
    - Use of other antivirals or other specific treatments for COVID 19

d) Deaths:

The number and percentage of patients who die within 7, 15 and 31 days after starting the treatment with plitidepsin will be described.

- From day 1 to day 7
- From day 8 to day 15
- From day 16 to day 31

In addition, cumulative table will be presented with the following groups:

- From day 1 to day 7
- From day 1 to day 15
- From day 1 to day 31

e) Oxygen therapy:

The number and percentage of patients requiring oxygen therapy on days 7, 15 y 31 after the start of plitidepsin treatment.

- From day 1 to day 7
- From day 8 to day 15
- From day 16 to day 31

In addition, cumulative table will be presented with the following groups:

- From day 1 to day 7
- From day 1 to day 15
- From day 1 to day 31

A descriptive table will be provided in which both variables are related to each of the variables indicated below at 4, 7, 15 and 31 days:

- Chronic lung disease (does not include asthma) (Yes; No).
- Oxygen therapy at baseline (Yes; No).
- Days from the onset of symptoms (continuous).
- Demographic characteristics (Age, Sex, Race)
- Baseline viral load (high, medium, low)
- FDA classification at baseline

A listing with the evolution of oxygen therapy in each of the controls performed on the patients, indicating the type of oxygen therapy (Room air; Oxygen therapy; Not available) and the flow will be provided.

Onset day of oxygen therapy from the onset day of symptoms, start of treatment with plitidepsin, start of treatment with corticosteroids reported in concomitant medication form.

f) Oxygen therapy (High flow):

High flow oxygen therapy is defined as the use of venturi mask or High Flow Nasal Cannula (HFNC) as oxygen therapy.

The number and percentage of patients requiring high flow oxygen therapy will be provided.

- From day 1 to day 7
- From day 8 to day 15
- From day16 to day 31

In addition, cumulative table will be presented with the following groups:

- From day 1 to day 7
- From day 1 to day 15
- From day 1 to day 31

Percentage of patients who change from low flow to high flow oxygen therapy.

g) Oxygen therapy (Low flow):

Low flow oxygen therapy is defined as the use of all oxygen therapy techniques except the ones use in high flow oxygen therapy.

The number and percentage of patients requiring low flow oxygen therapy will be provided.

- From day 1 to day 7
- From day 8 to day 15
- From day 16 to day 31.

In addition, cumulative table will be presented with the following groups:

- From day 1 to day 7
- From day 1 to day 15
- From day 1 to day 31

Percentage of patients who change from high flow to low flow oxygen therapy.

h) Mechanical ventilation (Invasive):

The following analysis will be performed:

- Total patients requiring Invasive Mechanical ventilation (95% IC)

- Number and percentage of patients requiring invasive mechanical ventilation
    - From day 1 to day 7
    - From day 8 to day 15
    - From day 16 to day 31

- In addition, cumulative table will be presented with the following groups:
    - From day 1 to day 7
    - From day 1 to day 15
    - From day 1 to day 31

- A descriptive table in which this variable is related to each of the variables indicated below at 4, 7, 15 and 31 days from the start of treatment will be provided:

- Chronic lung disease (does not include asthma) (Yes; No).
- Oxygen therapy at baseline (Yes; No).
- Days from onset of symptoms (continuous).

- If the patient has required invasive mechanical ventilation, the following analyses will be presented:
  - Number and percentage of patients who previously required non-invasive mechanical ventilation during the study.
  - Number and percentage of patients who previously required oxygen therapy during the study.
  - Number and percentage of patients with non-invasive mechanical ventilation after invasive mechanical ventilation.
  - Number and percentage of patients with oxygentherapy low/high flow after invasive mechanical ventilation.
- Onset day of IMV with respect to the days of onset of symptoms, start of treatment with plitidepsin, start of treatment with corticosteroids reported in concomitant medication form.
- Use of other specific COVID 19 treatments.
- Duration of invasive mechanical ventilation (continuous): The duration of invasive mechanical ventilation is defined as the time from the first day when invasive mechanical ventilation is used until invasive mechanical ventilation is removed.

i) Mechanical ventilation (Non-Invasive):

The following analysis will be performed:

- Total patients requiring Non-Invasive Mechanical ventilation (95% IC)
- Number and percentage of patients requiring non-invasive mechanical
  - From day 1 to day 7
  - From day 8 to day 15
  - From day 16 to day 31

- In addition, cumulative table will be presented with the following groups:
  - From day 1 to day 7
  - From day 1 to day 15
  - From day 1 to day 31

- Time of non-invasive mechanical ventilation (continuous): The duration of non-invasive mechanical ventilation is defined as the time from the first day when non-invasive mechanical ventilation is used until the non-invasive mechanical ventilation is removed.

- If the patient has required non-invasive mechanical ventilation, the following will be analyzed:
  - Number and percentage of patients who previously required invasive mechanical ventilation during the study.
  - Number and percentage of patients who previously required oxygen therapy during the study.

- Number and percentage of patients with invasive mechanical ventilation after non-invasive mechanical ventilation.
- Number and percentage of patients with oxygentherapy low/high flow after non-invasive mechanical ventilation.

- Onset day of NIMV from the onset day of symptoms, start of treatment with plitidepsin, start of treatment with corticosteroids.
- Use of other specific COVID 19 treatments

j) ICU admission:

The following variables will be analyzed:

- Total patients requiring ICU (95% IC)
- Number and percentage of patients requiring ICU admission since the start of treatment with plitidepsin.
    - From day 1 to day 7
    - From day 8 to day 15
    - From day 15 to day 31
- In addition, cumulative table will be presented with the following groups:
    - From day 1 to day 7
    - From day 1 to day 15
    - From day 1 to day 31

- A descriptive table in which this variable is related to each of the variables indicated below at 4,7, 15 and 31 days from the start of treatment will be provided:
    - Chronic lung disease (does not include asthma) (Yes; No).
    - Oxygen therapy at baseline (Yes; No).
    - Days from onset of symptoms (continuous)

- Time in ICU admission (continuous): The time in ICU is defined as the time, in days, from ICU admission to ICU discharge. It will be only calculated for those patients who have been admitted and discharged from the ICU.
- Onset day of ICU admission (continuous): Onset day of ICU admission is defined as the time, in days, from the date of the first dose of plitidepsin treatment to the date of admission to the ICU. It will only be calculated for those patients who have been admitted to the ICU.
- Use of corticosteroids and/or antiviral and other specific COVID 19 treatments
- Time from ICU admission to Hospital discharge (continuous): The time from ICU admission is defined as the time, in days, from the date of ICU admission to the date of discharge from the center. It will only be calculated for those patients who have been admitted and discharged from the ICU and have also been discharged from the center.Reason for ICU discharge (taken back to the ward; Death; Others).
- Invasive mechanical ventilation (Yes; No).
- Non-invasive mechanical ventilation (Yes; No).
- High flow oxygen therapy (Yes; No).

k) ICU admission or Mechanical ventilation (Invasive):

The following analysis will be performed:

- Number and percentage of patients requiring invasive mechanical ventilation or ICU admission since the start of treatment.
    - From day 1 to day 7
    - From day 8 to day 15
    - From day 16 to day 31
- In addition, cumulative table will be presented with the following groups:
    - From day 1 to day 7
    - From day 1 to day 15
    - From day 1 to day 31

l) Hospitalization:

The following variables will be analyzed:

- Hospital discharge (Yes / No). If not, a list of reasons will be provided.
- Time to Hospital discharge (continuous): The time to Hospital discharge is defined as the time, in days, from the date of treatment start and the date of hospital discharge. In those patients who have not been discharged, the time, in days, from the date of first dose to the last available date will be calculated and it will be censored for time to event analyses. The description of the variable will be done separately depending on whether the patient has been discharged from hospital or not. The median and 95% confidence interval will be presented.
- Time from admission to Hospital discharge (continuous): The time to Hospital discharge is defined as the time, in days, from the date of admission and the date of hospital discharge
- Multivariate analysis will be done to evaluate the relationship of the main covariates in the analysis with Hospital discharge on Day 8 (Yes/No) and Hospital discharge on Day15 (Yes/No) by means of logistic regression models. More relevant exploratory covariates from the univariate analyses (p-value < 0.10) will be included in the multivariate analyses.
- Multivariate analysis will be done to evaluate the relationship of the main covariates in the analysis with time to hospital discharge by means of Cox proportional hazard models. More relevant exploratory covariates from the univariate analyses (p-value < 0.10) will be included in the multivariate analyses.
- Swimmer plot Hospital Discharge Day by Viral Load at Baseline, Disease Severity at Baseline and oxygen (yes/no) at baseline.

m) Class at discharge:

The time to hospital discharge (category 1) at 6-points ordinal scale will be analyzed by the Kaplan-Meier method and the median and the 95% confidence interval will be provided.

The analysis will be completed by the following subgroups:

- FDA classification
- Oxygen therapy on day 1
- Symptoms evolution less or equal/greater than 6 days.

The value of the 6-point ordinal scale will be derived from CRF data by using the following definition:

1. Discharge (Alive)
2. Hospital admission, not requiring supplemental oxygen.
3. Hospital admission, requiring supplemental oxygen.
4. Hospital admission, requiring high-flow nasal cannula or non-invasive mechanical ventilation.
5. Hospital admission, requiring extracorporeal membrane oxygenation or invasive mechanical ventilation.
6. Death.

In addition, the following analyses will be performed:

- Distribution of patients on the 1st day of the administration of plitidepsin, and on days 7, 15 and 31 will be analyzed according to the 6-points ordinal scale value.
- Number and percentage of patients who improve at least one point on the scale on day 7, 15 and 31.
- Number and percentage of patients who improve at least two point on the scale on day 7, 15 and 31.
- Number and percentage of patients who improve at two point on the scale or are discharged (whichever comes first) on day 7, 15 and 31.

n) FDA risk groups

FDA risk groups will be derived from CRF data according to the following definition:

- Mild: if positive testing by standard RT-PCR assay or equivalent test, symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnoea, no clinical signs indicative of moderate, severe, or critical severity.
- Moderate: if positive testing by standard RT-PCR assay or equivalent test, symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion, clinical signs suggestive of moderate illness with COVID-19 such as respiratory rate ≥20 breaths per minute but <30 breaths per minute, SpO2 >93% but <95% on room air at sea level, heart rate ≥90 beats per minute but <125 beats per minute, no clinical signs indicative of severe or clinical illness severity.
- Severe: if positive testing by standard RT-PCR assay or equivalent test, symptoms of moderate illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress. Clinical of severe systemic illness with respiratory rate ≥30 breaths per minute, SpO2 ≤93% on room air at sea level, heart rate ≥90 beats per minute but ≥125 beats per minute or PaO2/FiO2 <300, no criteria for critical severity. Severinghaus equation was use to calculate PaO2/FiO2 as follow: paO2=(B+A)1/3 – (B-A)1/3 , where A=(11700)*(S-1 -1)-1 ; S= Oxygen saturation; B=(503 + A2)1/2 then PaO2/FiO2= PaO2/FiO2 *100. (See appendix VI)

The following analysis will be done according to FDA risk group (days of hospital admission, need for high-flow oxygen, NIMV, IMV, admission to the ICU).

Relationship between the baseline severity of the disease, the initial viral load and the time it takes to become negative.

Relationship between days of symptom evolution and disease severity.

Analysis of differences in inflammatory parameters (CRP, ferritin, transaminases, LDH) and hematological (lymphocytes) and level of viral load in patients according to the risk group of the FDA.

9 LISTINGS

The following data listings will be provided by patient and treatment arm for the total sample of patients included in the database.

9.1 Demographics, symptoms, and comorbidities data

The listing "Demographic, symptoms and comorbidities" will include the following information:

- Center
- Patient id.
- Dose.
- Age (years)
- Gender (Male/Female).
- Ethnic group
- Time from onset of first symptom
    - to hospital admission
    - to the administration of the first dose of plitidepsin
- Time from hospital admission to administration of the first dose of plitidepsin
- Fever history (Yes/No)
- Dehydration (Yes/No).
- Cough (Yes/No). In affirmative case, describe:
    - Sputum production (Yes/No). In affirmative case, describe:
        - Bloody sputum/ Hemoptysis (Yes/No).
- Runny nose (rhinorrhea) (Yes/No).
- Earache (Yes/No).
- Crackles (Yes/No).
- Thoracic pain (Yes/No).
- Muscular pain (myalgia) (Yes/No).
- Joint pain (arthralgia) (Yes/No).
- Fatigue / malaise (Yes/No).
- Short of breath (dyspnea) (Yes/No).
- Intercostal retraction (Yes/No).
- Headache (Yes/No).
- Altered state of consciousness / confusion (Yes/No).
- Convulsion (Yes/No).
- Abdominal pain (Yes/No).

- Vomiting / nausea (Yes/No).
- Diarrhea (Yes/No).
- Conjunctivitis (Yes/No).
- Rash (Yes/No).
- Skin ulcers (Yes/No).
- Lymphadenopathy (Yes/No).
- Throat pain (Yes/No).
- Bleeding (hemorrhage) (Yes/No). If so, the description of the bleeding locations will be detailed.
- Chronic cardiac pathologies including congenital cardiac pathologies (does not include hypertension) (Yes / No).
- Arterial hypertension (Yes/No).
- Chronic lung disease (does not include asthma) (Yes/No).
- Asthma (medical diagnosis) (Yes/No).
- Diabetes with complications (Yes/No).
- Diabetes without complications (Yes/No).
- Chronic kidney disease (Yes/No).
- Rheumatic disorder (Yes/No).
- Moderate or severe liver disease (Yes / No).
- Mild liver disease (Yes/No).
- Dementia (Yes/No).
- Malnutrition (Yes/No).
- Chronic neurological disorder (Yes / No).
- Smoker (Yes/No).
- Malignant neoplasm (Yes/No).
- Chronic hematological disease (Yes / No).
- AIDS / HIV (Yes / No).
- Obesity (define by medical staff) (Yes/No).
- Other risk factors (Yes / No). If so, the description of the specified factors will be detailed.
- SBP (mmHg) (continuous).
- DBP (mmHg) (continuous).
- Heart rate (b.p.m.) (continuous).
- Respiratory rate (b.p.m.) (continuous).
- Temperature (ºC) (continuous).
- Saturation O_2 (%) (continuous).
- Saturation (Room air/Oxygen therapy/Not available). In the case of oxygen therapy, the following will be described:

- Oxygen therapy type (Nasal glasses; Simple mask; Venturi mask; Reservoir mask; Other). In case of other a detailed listing will be provided.
- Flow (L/min) (continuous).
- FiO_2 (%) (continuous).
- PaO_2 (mmHg) (continuous)
- PaO_2/FiO_2 o SaO_2/FiO_2 (continuous).
- Chest X-ray (Yes/No). if so, the following will be described:
- X-ray result (Normal/Abnormal). In case of abnormality, the abnormality will be detailed (Unilateral Pneumonia / Bilateral Pneumonia / Other). In case of other abnormality, the description of the abnormalities will be provided.
- Electrocardiogram (Yes / No). If so, it will be described:
- Result (Normal / Abnormal: Not clinically significant or Abnormal: clinically significant). In case of abnormality, the description of the abnormalities will be provided. (QT interval prolongation / PR interval prolongation / other alteration). In case of other alteration, the description of the other alteration will be provided.

9.2 Screening failure

The listing "Screening failure" will include the following information

- Center
- Patient id.
- Screening failure (yes/no)
- Reason for selection failure (Inform consent withdrawal; Administration of prohibited medication; Death; Failure to comply with selection criteria).
    - Specific criteria, in case of the reason for selection failure is non-compliance with selection criteria.

9.3 Treatment

The listing “Treatment” will include the following information:

- Center
- Patient id.
- Treatment arm (Arm A; Arm B; Arm C)
- Treatment administration (Yes/No).
    - If so, reasons will be detailed.
- Administered doses
- Treatment interruption (Yes/No).
    - If so, the reasons will be indicated.
- Pre-medication (Yes/No). If so, it will be indicated:
    - Type (antiemetic, gastric protector, antihistamine and corticosteroids)
    - Code (ATC)

    - Active substance
    - Dose
    - Route of administration
- Units
- Days on treatment with plitidepsin
- Total dose of plitidepsin administered (sum of daily doses - mg)
- End of treatment date
- End of treatment (Treatment completed according to protocol; Withdraw informed consent; Non related adverse event; Adverse reaction to plitidepsin; Death; Investigator's decision; Administration of prohibited medication; Other).
    - If the adverse event is not related to the drug, the description of event and grade will be provided (1; 2; 3; 4; 5; Not available).
    - If the adverse event is related to the drug, the description of event and grade will be provided (1; 2; 3; 4; 5; Not available).
    - If it is Investigator's decision: specify
    - If other: specify

9.4 Adverse events

The listing "Adverse events" will include the following information:

- Center
- Patient id
- Treatment arm (Arm A; Arm B; Arm C)
- Age (<65 years; ≥ 65 years)
- Number of the adverse event
- Original term
- System (SOC)
- Preferred term (PT)
- Grade (1; 2; 3; 4; 5)
- Seriousness (Yes/No)
- Start date
- Ongoing
- End date
- Action taken (None; Treatment interruption; dose omitted; treatment withdrawal; Unknown)
- Relationship (Plitidepsin; Concomitant medication; Concomitant procedure; Related with study disease; Related with other disease; Other; Unknown)
    - Concomitant medication: specify.
    - Concomitant procedure: specify.
    - Related with other disease: specify.
    - Other: specify.

- Outcome (Recovered; Recovered with sequelae; Not recovered / Continues; Unknown; Death)
- Severity criteria (Death; Life-threatening; Requires hospitalization / Prolongation of hospitalization; Permanent or significant disability; Congenital anomaly or birth defect; Important medical event; transmission of an infectious agent via a medicinal product).
- Onset day: It is defined as the time, in days, from the start of treatment with plitidepsin to the date of onset of the adverse event. It will be specified for those adverse events related to plitidepsin.
- For plitidepsin-related adverse events of nausea or vomiting, additional information will be included regarding whether the patient exhibited such symptoms at the baseline visit and the administration of antiemetic prophylaxis at each of the plitidepsin doses.

9.5 Laboratory parameters

The listing "Laboratory parameters" will include the following information for baseline visit and day 3, 7, 15 y 31visits. The units, the percentage change from baseline and the result of each parameter will be specified. In the visit where the parameter is above the normal limit or below the normal limit is indicated, the clinically significant variable will be specified. Parameters will be standardized to equivalent units prior to data analysis.

- Center
- Patient id.
- Treatment arm (Arm A; Arm B; Arm C)
- Visit (Baseline, Day 3, Day 7, Day 15, Day 31)
- Date.
- Hematology:
    - Erythrocytes and units
    - Erythrocytes % change vs. Baseline
    - Hemoglobin and units
    - Hemoglobin % change vs. Baseline
    - Hematocrit and units
    - Hematocrit % change vs. Baseline
    - Platelets and units
    - Platelets % change vs. Baseline
    - Leukocytes and units
    - Leukocytes % change vs. Baseline
    - Neutrophils and units
    - Neutrophils % change vs. Baseline
    - Lymphocytes and units
    - Lymphocytes % change vs. Baseline
    - Lymphocytes-neutrophils relation
    - Lymphocytes-neutrophils % change vs. Baseline
    - Monocytes and units
    - Monocytes % change vs. Baseline

    - Eosinophils and units
    - Eosinophils % change vs. Baseline
    - Basophils and units
    - Basophils % change vs. Baseline

- Coagulation:
    - APTT/PTT and units
    - APTT/PTT % change vs. Baseline
    - PT and units
    - PT % change vs. Baseline
    - INR
    - D-dimer and units
    - D-dimer % change vs. Baseline
- Biochemistry:
    - Glucose and units
    - Glucose % change vs. Baseline
    - Alkaline phosphatase and units
    - Alkaline phosphatase % change vs. Baseline
    - Total Bilirubin and units
    - Bilirubin % change vs. Baseline
    - ALT and units
    - ALT % change vs. Baseline
    - AST and units
    - AST % change vs. Baseline
    - GGT and units
    - GGT % change vs. Baseline
    - LDH and units
    - LDH % change vs. Baseline
    - Creatinine and units
    - Creatinine % change vs. Baseline
    - CPK and units
    - CPK % change vs. Baseline
    - Ferritin and units
    - Ferritin % change vs. Baseline
    - Troponin and units
    - Troponin % change vs. Baseline
    - C-reactive protein and units

- C-reactive protein % change vs. Baseline

9.6 Other COVID-19 treatments

The listing "Other COVID-19 treatments" will include the following information including the baseline visit

- Center
- Patient id.
- Treatment arm (Arm A; Arm B; Arm C)
- COVID-19 Pharmacological treatment (Yes/No). If so, it will be described:
  - Chloroquine / Hydroxychloroquine (Yes / No).
  - Tocilizumab (Yes/No).
  - Remdesivir (Yes/No).
  - Lopinavir/Ritonavir (Yes/No).
  - IFN B 1b (Yes/No).
- Other pharmacological treatment (Yes/No). If so, a list per patient will be provided.
- Support treatment (Yes/No). If so, it will be described:
  - Antibiotics (Yes/No). If so, it will be described:
    - Azitromizina (Yes/No).
    - Other (Yes/No). If so, the specific treatment will be described
  - High-dose corticosteroids (excluding pre-medication) (Yes/No). If so, the specified treatment description will be described.
  - Antifungal agents (Yes / No). If so, the description of the specified treatment will be described.
  - Other support treatments (Yes / No). If so, the description of the specified treatment will be described.

Note: Information will only be provided for those patients receiving other COVID-19 drug treatment and/or supportive treatment at those visits where indicated.

The active substances provided will be coded including code (ATC) and term indicated in the database.

In the case of another pharmacological treatment for COVID-19 and/or support treatment with high-dose corticosteroids drugs, information about the time, in days, since the start of treatment with plitidepsin and the start of the other therapy, and the duration of the treatment will be provided

For corticosteroids, the daily dose received data will also be provided.

9.7 Concomitant medication/procedure

The listing "Concomitant medication/procedure" will include the following information:

- Center
- Patient id.
- Treatment arm (Arm A; Arm B; Arm C)

- Medication / procedure (Yes/no)
- Medication / procedure description
- Use (Prophylactic; Therapeutic)
- Description: Active substance/Procedure
- Code (ATC)
- Start date
- Ongoing (Yes/No)

- End date
- Dose
- Units (mg; µg; mL; g; IU; Other)
    - Other: specify
- Frequency (2 times a day; 3 times a day; 4 times a day; A demand; Every 24 hours; Monthly Weekly; Daily; Every hour; Every 2 hours; Other)
    - Other: specify
- Route of administration (Oral; Topical; Subcutaneous; Transdermal; Intraocular; Intramuscular; Intravenous; Respiratory (inhaled); Intraperitoneal; Nasal; Other.)
    - Other: specify
- Indication (study disease; Concomitant disease; Adverse event; Other)
    - Adverse event: specify
    - Other: specify

9.8 End of study

The listing "End of study" will include the following information:

- Center
- Patient id.
- Treatment arm (Arm A; Arm B; Arm C)
- End of study (yes/no)
- End of study reason (Follow-up completed according to protocol; Withdrawal by subject; Lost to Follow-up; Death; the patient was randomized but did not receive the study drug; Investigator's decision; Early end of study; Other).
    - Lost to Follow-up: date.
    - The patient was randomized but did not receive the study drug: specify.
    - Investigator's decision: specify.
    - Early end of study: specify.
    - Other: specify.
- Follow-up time: defined as the time, in days, between the informed consent signing date until the end of study date by the patient. If the study has not been completed at the time of the analysis, the date of the last follow-up of the patient will be taken.

9.9 Deaths

The listing "Deaths" will include the following information:

- Center
- Patient id.
- Treatment arm (arm A; Arm B; Arm C)
- End of treatment (yes/no)

- Main cause of death (Acute respiratory distress syndrome (ARDS); Adverse event not related to treatment; Adverse reaction to plitidepsin; Unknown; Other)
    - Adverse event not related to treatment: the description of the event and the grade (1; 2; 3; 4; 5; Not available) will be provided.
    - Adverse reaction to plitidepsin, description of toxicity and grade will be provided (1; 2; 3; 4; 5; Not available).
    - Other: specify

9.10 Protocol deviations

The listing will include the following information:

- Center
- Deviation date
- Related patient
- Category (Minor; Major; Critical)
- Deviation (Selection criteria; Informed consent; Investigational drug; Safety; Efficacy criteria; Others)
- Reason (text)

APPENDIX I

10 STUDY POPULATION

10.1 Patient disposition

Table 10.1.1 Subject Disposition

Disposition	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Included Population				
Safety Population				
Efficacy Population				
Completed 3-day treatment				
Completed Day 31 follow-up				

Listing 10.1.2 Patients included but not treated.

Patient id.	Description

Table 10.1.3 Subject Disposition by site

Sites	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
	n (%)							
	Included	Treated	Included	Treated	Included	Treated	Included	Treated
Site 1								
Site 2								
Site …								

Table 10.1.4 Study dates

	Total
Date of first registration	
Date of first dose of the first patient	
Date of last registration	
Date of first dose of the last patient	
Date of last dose	
Date of last follow-up*	

(*) Last follow-up, exam or procedure before clinical cut-off or study closure

Table 10.1.5 Treatment discontinuation

Reason	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Primary reason for treatment discontinuation prior to Day 31 safety follow-up:				
Adverse event				
Death				
…				

Table 10.1.6 Off-study

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Off study reasons				
Completed				
Lost to Follow -up				
Withdrawal of consent				
…				

10.2 Patient description

Table 10.2.1 Demographic and Other Baseline Characteristics

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Age, median (range) years				
Gender, % male				
Median (range) time from symptom onset to first administration, days				
Number of comorbidities, n (%)				
None				
One				
Two or more				
Comorbidities, n (%)				
Cardiac disease				
Kidney disease				
Liver disease				
Lung disease (COPD)				
Asthma				
Diabetes				
Hypertension				
Obesity				
Clinical status at baseline, n (%)				
Mild COVID-19 infection				
Moderate COVID-19 infection				
Severe COVID-19 infection				
Vital signs, median (range)				
Body temperature, °C				
Systolic blood pressure, mmHg				
Diastolic blood pressure, mmHg				
Heart rate, bpm				
Respiratory rate, bpm				
SpO_2 at room air, %				
On oxygen at baseline, n (%)				
Laboratory parameters, median (range)				
WBC, $x10^9$/L				
Platelet count, $x10^9$/L				
Lymphocytes, $x10^9$/L				
Serum creatinine, µmol/L				
ALT, x ULN				
AST, x ULN				
LDH, x ULN				

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
GGT, x ULN				
CPK, x ULN				
Ferritin (ng/mL)				
D-dimer (ng/mL)				
C-reactive protein (mg/L)				
log_{10} viral load, median (range) copies/mL				

(*) Further covariates could be added upon request

Table 10.2.2 Demographic Baseline Characteristics (continuous variables)

	Dose Cohort																	
	1.5						…						Total					
	N	Mean	Median	Range	Q1	…*	…	…	…	…	…	…	N	Mean	Median	Range	Q1	…*
Age																		

(*) Q3 and Std.

Table 10.2.3 Clinical data *(*Signs and symptoms on admission) Baseline Characteristics (continuous variables)

	Dose Cohort																	
	1.5						…						Total					
	N	Mean	Median	Range	Q1	…*	…	…	…	…	…	…	N	Mean	Median	Range	Q1	…*
**																		

(*) Q3 and Std.
(**)Onset first symptom to signing of IC; Onset first symptom to first dose of treatment, Onset first symptom to first PCR

Table 10.2.4 Vital signs Baseline Characteristics (continuous variables)

	Dose Cohort																	
	1.5						…						Total					
	N	Mean	Median	Range	Q1	…*	…	…	…	…	…	…	N	Mean	Median	Range	Q1	…*
**																		

(*) Q3 and Std.
(**) SBP, DBP, Heart rate, Respiratory rate, Temperature, Saturation O2, Flow FiO2, PaO2, PaO2/FiO2 or SaO_2/FiO_2

Table 10.2.5 Demographic Baseline Characteristics (categorical variables)

n (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
*				

(*) Gender (Male/Female); Age (<65/>=65); Ethnic group

Table 10.2.6 Clinical data *(*Signs and symptoms on admission) Baseline Characteristics

n (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
*				

(*) Time from the beginning of the first symptom to hospital admission, Time from hospital admission to first dose of plitidepsin treatment, Fever, Dehydration, Cough, Sputum production, Hemoptysis, Runny nose, Earache, Crackles, Thoracic Pain, Muscular pain, Joint pain, Fatigue, Short of breathe, Intercostal retraction, Headache, Confusion, Convulsion, Abdominal pain, Vomiting\Nausea, Diarrhea, Conjunctivitis, Rash, Skin ulcer, Lymphadenopathy, Throat pain, Bleeding.

Table 10.2.7 Clinical data (Comorbidities) Baseline Characteristics (categorical variables)

n (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
*				

(*)Chronic Cardiac pathologies, Arterial Hypertension, Chronic lung disease, Asthma, Diabetes with complications, Diabetes without complications, Chronic kidney disease, Rheumatic disorder, Moderate or severe liver disease, Mild liver disease, Dementia, Malnutrition, Chronic neurological disorder, Smoker, Malignant neoplasm, Chronic hematological disease, AIDS, obesity, Other risk factors, Other details.

Table 10.2.8 Vital signs at baseline Characteristics (categorical variables)

n (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
*				

(*) Saturation, Oxygen therapy type, Chest X-Ray, Electrocardiogram, Result, FDA classification

Table 10.2.9 Six-point ordinal scale on Day 1

n (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
1 Discharge (Alive)				
2 Hospital admission, not requiring supplemental oxygen				
…				

Table 10.2.10 Days with symptoms according to baseline viral load

	Viral Load at baseline (copies/mL)			
	Low <4	Medium [4-7]	High >7	p-value(*)
Days with symptoms				

(*) Kruskal-Wallis

APPENDIX II

11 SAFETY EVALUATION

11.1 Safety endpoints

Table 11.1.1 Summary of Protocol-Specified Safety Endpoints. Cumulative results.

Endpoint	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Patients unable to complete treatment				
Patients with grade ≥3 AEs from Day 1 to				
Day 3				
Day 7				
Day 15				
Day 31				
Patients with AEs from Day 1 to				
Day 3				
Day 7				
Day 15				
Day 31				
Patients with SAEs from Day 1 to				
Day 3				
Day 7				
Day 15				
Day 31				
Patients with ≥ 1 grade change in hematological parameters from Day 1 to				
Day 3				
Day 7				
Day 15				
Day 31				
Patients with ≥ 1 grade change in non-hematological parameters, from Day 1 to				
Day 3				
Day 7				
Day 15				
Day 31				
Patients with QTc >60msec from baseline to				
Day 31				

This table will be also performed by age (<65 vs. >=65 year old (11.1.1.1)

Table 11.1.2 Summary of Protocol-Specified Safety Endpoints. Non-cumulative.

Endpoint	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Patients unable to complete treatment				
Patients with grade ≥3 AEs from				
Day 1 to Day 3				
Day 4 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients with AEs from				
Day 1 to Day 3				
Day 4 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients with SAEs from				
Day 1 to Day 3				
Day 4 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients with ≥ 1 grade change in hematological parameters from				
Day 1 to Day 3				
Day 4 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients with ≥ 1 grade change in non-hematological parameters, from				
Day 1 to Day 3				
Day 4 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				

This table will be also performed by age (<65 vs. >=65 year old (11.1.2.1)

11.2 Treatment administration

Table 11.2.1 Administered Doses

Administered Doses, n (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Day1				
Day 2				
Day 3				

This table will be also performed by age (<65 vs. >=65 year old) (11.2.1.1)

Table 11.2.2 Administered dose interrupted

Administered dose interrupted	1.5 mg		2 mg		2.5 mg		Total	
	N	%	N	%	N	%	N	%
Reason								

This table will be also performed by age (<65 vs. >=65 year old) (11.2.2.1)

Table 11.2.3 Total administered dose

	Dose Cohort																	
	1.5						…						Total					
	N	Mean	Median	Range	Q1	…#	…	…	…	…	…	…	N	Mean	Median	Range	Q1	…*
Total dose (mg)																		

This table will be also performed by age (<65 vs. >=65 year old) (11.2.3.1)

Table 11.2.4 Relative dose intensity

	Dose Cohort																	
	1.5						…						Total					
	N	Mean	Median	Range	Q1	…#	…	…	…	…	…	…	N	Mean	Median	Range	Q1	…*
Relative dose intensity (%)																		

This table will be also performed by age (<65 vs. >=65 year old) (11.2.4.1)

11.3 Premedication

Table 11.3.1 Administered Premedication

Premedication		1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
		N	%	N	%	N	%	N	%
Day 1	Yes								
Day 2	Yes								
Day 3	Yes								

Table 11.3.2 Premedication

Premedication*		1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
		N	%	N	%	N	%	N	%
ATC1	ATC2								
	ATC2								
ATC1	ATC2								

(*)More ATC levels could be displayed upon request.

11.4 Adverse events

Table 11.4.1 Summary of Adverse Events, Regardless of Relationship, by SOC and PT by Dose Cohort and Overall

MedDRA SOC Preferred Term	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Subjects with any AE				
Gastrointestinal disorders				
Abdominal pain				
Abdominal pain upper				
….				
General disorders and administration site conditions				
Asthenia				
Chest discomfort				
…				

Each patient reported once per Preferred Term; This table will be also performed by age (<65 vs. >=65 year old) (11.4.1.1)

Listing 11.4.2 All adverse events

Dose cohort	Subject id.	Age	SOC	PT	Serious adverse events	Relationship	Grade	Onset date	End date

Table 11.4.3 Summary of Treatment-Related Adverse Events by SOC and PT by Dose Cohort and Overall

MedDRA SOC Preferred Term	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Subject with any related AE				
Gastrointestinal disorders				
Abdominal pain				
Abdominal pain upper				
….				
General disorders and administration site conditions				
Asthenia				
Chest discomfort				
…				

Each patient reported once per Preferred Term; This table will be also performed by age (<65 vs. >=65 year old) (11.4.3.1)

Listing 11.4.4 All Related Adverse Events

Dose cohort	Subject id.	Age	SOC	PT	Serious adverse events	Relationship	Grade	Onset date	End date

Table 11.4.5 Grade ≥3 Adverse Events, Regardless of Relationship by Dose Cohort and Overall

MedDRA SOC Preferred Term	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Patients with any Grade ≥3 AE				
Blood and lymphatic system disorders				
Leukocytosis				
Gastrointestinal system disorders				
Diarrhea				

Each patient reported once per Preferred Term; This table will be also performed by age (<65 vs. >=65 year old) (11.4.5.1)

Table 11.4.6 Summary of Treatment-Related Adverse Events by SOC and PT by grade and Overall. Worst grade per patient.

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

This table will be also performed by pre & post amendment (13AUG2020) (11.4.6.1)

This table will be also performed by pre & post amendment (11SEP2020) (11.4.6.2)

Table 11.4.7 Summary of Treatment-Related Adverse Events by SOC and PT by grade and Overall. Worst grade per patient. (Dose 1.5 mg)

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

Table 11.4.8 Summary of Treatment-Related Adverse Events by SOC and PT by grade and Overall. Worst grade per patient. (Dose 2 mg)

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

Table 11.4.9 Summary of Treatment-Related Adverse Events by SOC and PT by grade and Overall. Worst grade per patient. (Dose 2.5 mg)

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

Table 11.4.10 Summary of Adverse Events Regardless of Relationship by SOC and PT by grade and Overall. Worst grade per patient.

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

This table will be also performed by pre & post amendment (13AUG2020) (11.4.10.1)

This table will be also performed by pre & post amendment (11SEP2020) (11.4.10.2)

Table 11.4.11 Summary of Adverse Events, Regardless of Relationship by SOC and PT by grade and Overall. Worst grade per patient. (Dose 1.5 mg)

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

Table 11.4.12 Summary of Adverse Events, Regardless of Relationship by SOC and PT by grade and Overall. Worst grade per patient. (Dose 2 mg)

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

Table 11.4.13 Summary of Adverse Events, Regardless of Relationship by SOC and PT by grade and Overall. Worst grade per patient. (Dose 2.5 mg)

Drug Related AEs		G1		G2		G3		….		Total	
		N	%	N	%	N	%	N	%	N	%
Gastrointestinal disorders	Abdominal pain										
	…										
	…										
	….										

Table 11.4.14 Summary of Adverse Events

Patients	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
	N	%	N	%	N	%	N	%
Patients with AEs								
Patients with treatment-related AEs								
Patients with Grade >=3 AEs								
Patients with Grade >=3 treatment-related AEs								
Patients with SAEs								
Patients with treatment-related SAEs								

This table will be also performed by age (<65 vs. >=65 year old) (11.4.14.1)

Listing 11.4.15 Patients Experiencing AEs Leading treatment discontinuation or drug interruption

Dose Cohort	Subject id	Sex	Age	AE treatment discontinuation/Interruption	Relatedness	Study Day of Onset/Death

11.5 Serious Adverse events and Death

Listing 11.5.1 SAEs Regardless of Relationship

Dose cohort	Subject id.	Age	SOC	PT	Relationship	Grade	Onset date	End date

Listing 11.5.2 SAEs Related

Dose cohort	Subject id.	Age	SOC	PT	Relationship	Grade	Onset date	End date

Listing 11.5.3 Patients Experiencing SAEs Leading treatment discontinuation

Dose Cohort	Subject id	Sex	Age	TEAE treatment discontinuation	Relatedness	Study Day of Onset/Death

Listing 11.5.4 Patients Experiencing Serious Adverse Events (SAEs) Not Resulting in Death

Dose Cohort	Subject id	Sex	Age	SAE event	Action	Relatedness	Study Day of Onset/Resolution

Table 11.5.5 Death

Death n (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Death				

Listing 11.5.6 Patients Experiencing SAEs Leading to Death

Dose Cohort	Subject id	Sex	Age	TEAE Leading to Death	Relatedness	Day of Death

11.6 Laboratory

Table 11.6.1 Shift in Hematology Parameters from Baseline to Greatest Change in Grade on Study for Combined Dose Groups

Parameter	Grade at Baseline	Grade Change per Patient on Study				
		0	1	2	3	Total
Anemia (hemoglobin)	0					
	1					
Leukopenia (leukocytes)	0					
	1					
	…					
…….						

This table will be also performed by age (<65 vs. >=65 year old) (11.6.1.1)

This table will be also performed by inflammatory parameters (11.6.1.2)

Laboratory table by pre&post amendment (13AUG2020) will be generated upon request. (11.6.1.3)

This table will be also performed by pre&post amendment (13AUG2020) (11.6.1.4)

Table 11.6.2 Shift in Chemistry Parameters from Baseline to Greatest Change in Grade on Study for Combined Dose Groups Percentages are shown for changes from baseline

Parameter	Grade at Baseline	Grade Change per Patient on Study				
		0	1	2	3	Total
ALT increased	0					
	1					
AP increased	0					
	missing					
AST increased	0					
	1					
……..	……					

This table will be also performed by age (<65 vs. >=65 year old) (11.6.2.1)

This table will be also performed by pre&post amendment(13AUG2020) (11.6.2.2)

Listing 11.6.3 Hematological laboratory parameters

Subject ID	Visit	Date	…(*)	change (%)	…()	change (%)
…..	Baseline					
	Day 3					
	…					

(*) Hematological parameters

Listing 11.6.4 Coagulation laboratory parameters

Subject ID	Visit	Date	…(*)	change (%)	…()	change (%)
…..	Baseline					

Subject ID	Visit	Date	…(*)	change (%)	…()	change (%)
	Day 3					
	…					

(*) Coagulation parameters

Table 11.6.5 Biochemical laboratory parameters

Subject ID	Visit	Date	…(*)	change (%)	…()	change (%)
…..	Baseline					
	Day 3					
	…					

(*) Biochemical parameters

Listing 11.6.6 Laboratory abnormalities reported in AE form

Dose Cohort	Subject id	AE	PT	SOC	Action	Relatedness	Study Day of Onset/Resolution

11.7 Vital sings, ECG and Chest X-Ray

Table 11.7.1 Change in Vital Signs from Baseline through Day 31

Parameter*	**Dose Cohort**			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Blood pressure, diastolic (mm Hg), median (range)				
Baseline				
Change at Day 1				
Change at Day 2				
Change at Day 3				
Change at Day 7				
Change at Day 15				
Change at Day 31				
Blood pressure, systolic (mm Hg), median (range)				
Baseline				
Change at Day 1				
Change at Day 2				
Change at Day 3				
Change at Day 7				
Change at Day 15				
Change at Day 31				
Heart rate (beats per minute), median (range)				
Baseline				
Change at Day 1				
Change at Day 2				
Change at Day 3				
Change at Day 7				
Change at Day 15				
Change at Day 31				
Respiratory rate (breaths per minute), median (range)				
Baseline				
Change at Day 1				
Change at Day 2				
Change at Day 3				
Change at Day 7				
Change at Day 15				
Change at Day 31				
pSO2** by pulse oximetry (%), median (range)				
Baseline				
Change at Day 1				
Change at Day 2				

Change at Day 3				
Change at Day 7				
Change at Day 15				
Change at Day 31				

This table will be also performed by age (<65 vs. >=65 year old) (11.7.1.1)

(*) Mean value of the different measurement per day will be used for blood pressure. Worst value per patient, per day, will be used for the rest of measurements for the analysis.

(**) Room-air.

Table 11.7.2 ECG and Chest X-ray

Endpoint	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Patients with abnormal Chest X-ray, n (%)				
Day 1				
Day 2…				
Day 31				
Patients with bilateral pneumonia, n (%)				
Day 1…31				
Patients with abnormal no significative ECG, n (%)				
Day 1…31				
Patients with abnormal significative ECG, n (%)				
Day 1…31				

This table will be also performed by age (<65 vs. >=65 year old) (11.7.2.1)

Table 11.7.3 Chest X-ray evolution

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
Chest X-ray improvement, n (%)				
Day 7				
Day 15				
Day 31				
Chest X-ray worsening, n (%)				
Day 7				
Day 15				
Day 31				
Chest X-ray no changes, n (%)				
Day 7				
Day 15				
Day 31				

This table will be also performed by age (<65 vs. >=65 year old) (11.7.3.1)

Listing 11.7.4 Chest X-ray

Subject ID	Visit	Date	Results	Abnormal result	Abnormal: Other	Change	Change result

Table 11.7.5 Shift in QTc Data from Baseline to Worst Result on Treatment

Baseline Result	Worst Post-Baseline Result						
	Normal	QTc >450ms	QTc >480ms	QTC >500ms	QTc >30ms from baseline	Other abnormality	Total
Combined cohorts:							
Normal							
QTc>450ms							
QTc>480ms							
QTc>500ms							
Other abnormality							
Total							

This table will be also performed by age (<65 vs. >=65 year old) (11.7.5.1)

Listing 11.7.6 SaO2 evolution

Subject ID	Visit	Date	Time	Type of oxygen saturation	SaO2 (%)
	Baseline		….	….	
	Day 1		…	Room air	

11.8 Concomitant medication

Table 11.8.1 Concomitant medication ATC1*ATC2

ATC codes	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
ATC1				
ATC2				
ATC2				
ATC1				
ATC2				

Table 11.8.2 Concomitant medication ATC1*ATC2*ATC4*PN

ATC1 ATC2	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
ATC1				
ATC2				
ATC4				
PN				
ATC1				
ATC2				
ATC4				
PN				

Table 11.8.3 Requirement of another specific treatment for COVID-19

Specific treatment for COVID-19	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
	N	%	N	%	N	%	N	%
Yes								
No								

Table 11.8.4 Support treatment requirements

Support treatment requirements	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
	N	%	N	%	N	%	N	%
Yes								
No								

Table 11.8.5 Support treatment ATC1*ATC2*ATC4

Support treatment	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
	n (%)			
ATC1*ATC2*ATC4				

Table 11.8.6 Concomitant treatment duration

Days	Dose Cohort																	
	1.5						…						Total					
	N	Mean	Median	Range	Q1	…*	…	…	…	…	…	…	N	Mean	Median	Range	Q1	…*
Corticosteroids treatment																		
Antibiotic treatment																		

(*) Q3 and Std.

APPENDIX III

12 EFFICACY EVALUATION

12.1 Efficacy evaluation

Table 12.1.1 Number of patients with PCR

Number of patients with PCR	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Baseline				
Undetectable				
Positive				
Day …				

Table 12.1.2 Viral load classification by dose level and total

Day	Viral Load at baseline (copies/mL)	Viral Load classification during treatment (copies/mL)			
		Low <4	Medium [4-7]	High >7	Total
Day 4	Low <4				
	Medium [4-7]				
	High >7				
	Total				
…(*)	Low <4				
	Medium [4-7]				
	High >7				
	Total				

(*) Days 7, 15 and 31

Listing 12.1.3 Viral load evolution

Subject id	Dose	Visit	Result	log10 viral load copies/mL

Table 12.1.4 Summary of Protocol-Specified Efficacy Endpoints. Cumulative results.

Endpoint from day 1to	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Patients discharged from hospital, n (%)				
Day 7				
Day 8				
Day 15				
Day 31				
Deaths at, n (%)				
Day 7				
Day 15				
Day 31				
Later than Day 31				
Patients requiring invasive mechanical ventilation and/or ICU admission at, n (%)				
Day 7				
Day 15				
Day 31				
Patients requiring invasive mechanical ventilation, n (%)				
Day 7				
Day 15				
Day 31				
Patients requiring ICU admission at, n (%)				
Day 7				
Day 15				
Day 31				
Patients requiring non-invasive mechanical ventilation at, n (%)				
Day 7				
Day 15				
Day 31				
Patients requiring oxygen therapy at, n (%)				
Day 7				
Day 15				
Day 31				
Patients requiring oxygen therapy (high flow) at, n (%)				
Day 7				
Day 15				
Day 31				
Patients requiring oxygen therapy (low flow) at, n (%)				
Day 7				
Day 15				
Day 31				

This table will be also performed by age (<65 vs. >=65 year old (12.1.4.1)
This table will be also performed by FDA classification (12.1.4.2)

Table 12.1.5 Summary of Protocol-Specified Efficacy Endpoints. Non-cumulative results.

Endpoint	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Patients discharged from hospital, n (%)				
Day 1 to Day 8				
Day 9 to Day 15				
Day 16 to Day 31				
Deaths at, n (%)				
Day 1 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Later than Day 31				
Patients requiring invasive mechanical ventilation and/or ICU admission at, n (%)				
Day 1 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients requiring invasive mechanical ventilation, n (%)				
Day 1 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients requiring ICU admission at, n (%)				
Day 1 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients requiring non-invasive mechanical ventilation at, n (%)				
Day 1 to Day 7				
Day 8 to Day 15				
Day 16 to Day 31				
Patients requiring oxygen therapy at, n (%)				
Day 1 to Day 7				
Day 15				
Day 31				
Patients requiring oxygen therapy (high flow) at, n (%)				
Day 7				
Day 15				
Day 31				
Patients requiring oxygen therapy (low flow) at, n (%)				
Day 7				
Day 15				
Day 31				

This table will be also performed by age (<65 vs. >=65 year old) (12.1.5.1)
This table will be also performed by FDA classification (12.1.5.2)

Table 12.1.6 Summary of Protocol-Specified Efficacy Endpoints 95%CI

Dose Cohort																
1.5 mg				2 mg				2.5 mg				Total				
N	%	Exact CI Lower	Exact CI Upper	N	%	Exact CI Lower	Exact CI Upper	N	%	Exact CI Lower	Exact CI Upper	N	%	Exact CI Lower	Exact CI Upper	

(*) Patients requiring Invasive Mechanical Ventilation; Patients requiring Non Invasive Mechanical Ventilation; Patients requiring ICU.

This table will be also performed by age (<65 vs. >=65 year old (12.1.6.1)
This table will be also performed by FDA classification (12.1.6.2)

Table 12.1.7 Viral load change from baseline and negative detection

Mean change in viral load from baseline to, log10 copies/mL	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Day 4				
Day 7				
Day 15				
Day 31				
Mean time from baseline until undetectable viral load (days)*				

All patients (12.1.7.1), Mild & moderate patients (12.1.7.2), moderate patients (12.1.7.3), severe patients (12.1.7.4).
(*) From baseline PCR

Table 12.1.8 Viral load at baseline and study outcome variables

	Viral Load at baseline			
	Low <4	Medium [4-7]	High >7	p-value(*)
Oxygen therapy				
Yes				
No				
Oxygen therapy Low flow				
Yes				
No				
Oxygen therapy High flow				
Yes				
No				
ICU admission				
Yes				
No				
NIMV				
Yes				
No				
IMV				
Yes				
No				
Death				
Yes				
No				
Days of hospitalization				
FDA Risk groups				
Mild				
Moderate				
Severe				

(*)Fisher's exact test for categorical variables. Kruskal-Wallis test for continuous variables.

Table 12.1.9 Patients with negative detection

Number of patients (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Day 4				
Day 7				
Day 15				
Day 31				

Table 12.1.10 Patients with negative detection according to initial viral load

Number of patients (%)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Low <4				
Medium [4-7]				
High >7				
Total				

Table 12.1.11 Time to negative detection

Time to negative detection	Time to negative detection			
	N	Median	Range	p-value(**)
Viral load at baseline				
Low <4				
Medium [4-7]				
High >7				
Dose				
1.5 mg				
2.0 mg				
2.5 mg				
Age				
< 65 y.o.				
>=65 y.o				
Sex				
Female				
Male				
Race				
White				
Other				
… (*)				

(*) FDA risk groups (Mild, moderate, severe), Oxygen need (Yes/No), Chronic lung disease (Yes/No), Corticosteroids (Yes/No), Other antiviral treatment for COVID-19 (Yes/No). Further variables could be added upon request

(**) Kruskal-Wallis

Table 12.1.12 Time to negative detection by corticosteroid duration

Time to negative detection	Corticosteroid duration		
	< 10 days	>= 10 days	p-value*
Dose			
1.5 mg			
2.0 mg			
2.5 mg			
Total			

(**) Kruskal-Wallis

Table 12.1.13 Oxygen therapy

Number of patients (%)	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
	Oxygen therapy							
	Yes	No	Yes	No	Yes	No	Yes	No
Oxygen therapy at baseline								
Yes								
No								
Chronic Lung Disease								
Yes								
No								
Age								
< 65 y.o.								
>=65 y.o								
Gender								
Female								
Male								
Race								
White								
Other								
Viral load at baseline								
Low <4								
Medium [4-7]								
High >7								
FDA Risk groups								
Mild								
Moderate								
Severe								

Listing 12.1.14 Oxygen therapy evolution

Subject id	Dose	Visit	Date	Time	Oxygen therapy type	Flow

Table 12.1.15 Oxygen therapy onset day

Onset day	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
From start of symptoms								
From first plitidepsin dose								
From corticosteroids use								

Table 12.1.16 Patients changing oxygen therapy

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
From no Oxygen therapy to Oxygen therapy				
From low flow to high flow				
From high flow to low flow				

Table 12.1.17 Time in (ICU- Invasive M Ventilation – Non Invasive MV – in Hospital)

Time (days)	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
ICU				
Invasive mechanical ventilation				
Non Invasive mechanical ventilation				
Hospital*				

(*)From first infusion

Table 12.1.18 Reason for ICU discharge

Endpoint	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Reason for ICU discharge, n (%)				
Taken back to the ward				
Death				

Table 12.1.19 ICU admission according to oxygen therapy or chronic lung disease

Number of patients (%)	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
	ICU admission*							
	Yes	No	Yes	No	Yes	No	Yes	No
Oxygen therapy at baseline								
Yes								
No								
Chronic Lung Disease								
Yes								
No								

(*) on day 7, 15 and 31.

Table 12.1.20 ICU admission

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Antiviral, n (%)				
Yes				
No				
Use of corticosteroids, n (%)				
Yes				
No				
Other COVID-19 treatment, n (%)				
Yes				
No				
High flow oxygen				
Yes				
No				
Invasive mechanical ventilation, n (%)				
Yes				
No				
Non-invasive mechanical ventilation, n (%)				
Yes				
No				

Table 12.1.21 ICU admission onset day and time to hospital discharge

Onset Day	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
From first plitidepsin dose								
From onset of symptoms								
From ICU admission to hospital discharge								

Table 12.1.22 Hospital discharge

Endpoint	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Hospital discharge, n (%)				
Yes				
No				
Reason				

Table 12.1.23 Time to Hospital discharge

Days	Dose Cohort			
	1.5 mg Median (range)	2.0 mg Median (range)	2.5 mg Median (range)	Total Median (range)
From first dose				
From admission				

Table 12.1.24 Multivariate analysis Hospital discharge on day 8

Variable	Value	DF	Estimate	Standard error	Wald Chi-Square	Pr > Chi-Square	Effect	Odds Ratio Estimate	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio
..										

(*) Logistic regression.

Table 12.1.25 Multivariate analysis Hospital discharge on day 15

Variable	Value	DF	Estimate	Standard error	Wald Chi-Square	Pr > Chi-Square	Effect	Odds Ratio Estimate	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio
..										

(*) Logistic regression.

Table 12.1.26 Multivariate analysis Time to hospital discharged

Parameter	DF	Parameter Estimate	Standard error	Chi-Square	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	Pr > ChiSq
…								

(*) Cox regression.

Table 12.1.27 Invasive mechanical ventilation

Number of patients (%)	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
	Invasive mechanical ventilation*							
	Yes	No	Yes	No	Yes	No	Yes	No
Oxygen therapy at baseline								
Yes								
No								
Chronic Lung Disease								
Yes								
No								

(*) at day 4, 7, 15 and 31.

Table 12.1.28 Invasive mechanical ventilation with prior/further non-invasive mechanical ventilation or oxygen therapy

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Prior Non-invasive mechanical ventilation, n (%)				
Yes				
No				
Further Non-invasive mechanical ventilation, n (%)				
Yes				
No				
Prior oxygen therapy, n (%)				
Yes				
No				
Further oxygen therapy, n (%)				
Yes				
No				
Further oxygen therapy Low flow, n (%)				
Yes				
No				
Further oxygen therapy High Flow, n (%)				
Yes				
No				
Other COVID-19 treatment, n (%)				
Yes				
No				

Table 12.1.29 Invasive mechanical ventilation onset day

Onset day	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
From start of symptoms								
From first plitidepsin dose								
From corticosteroids use								

Table 12.1.30 Non-invasive mechanical ventilation with prior invasive mechanical ventilation or oxygen therapy

	Dose Cohort			
	1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Prior invasive mechanical ventilation, n (%)				
Yes				
No				
Oxygen therapy, n (%)				

Yes				
No				
Other COVID-19 treatment, n (%)				
Yes				
No				

Table 12.1.31 Non-invasive mechanical ventilation onset day

Onset day	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
From start of symptoms								
From first plitidepsin dose								
From corticosteroids use								

Table 12.1.32 Six-point ordinal scale

Treatment day	n (%)	Dose Cohort			
		1.5 mg N=X	2.0 mg N=X	2.5 mg N=X	Total N=X
Day 7	1 Discharge (Alive)				
	2 Hospital admission, not requiring supplemental oxygen				
	…				
Day …*	1 Discharge (Alive)				
	2 Hospital admission, not requiring supplemental oxygen				
	…				

(*) On days 15 and 31

Table 12.1.33 Six-point ordinal scale shift table

Treatment day	Baseline 6-point ordinal scale	6-point ordinal scale			
		1 Discharge (Alive)	2 Hospital admission, not requiring supplemental oxygen	…	Total
Day 7	1 Discharge (Alive)				
	2 Hospital admission, not requiring supplemental oxygen				
	…				
Day …*	1 Discharge (Alive)				
	2 Hospital admission, not requiring supplemental oxygen				
	…				

(*) On days 15 and 31. It could be done by dose, if requested.

Table 12.1.34 Two points improvement in Six-point ordinal scale or discharged by day

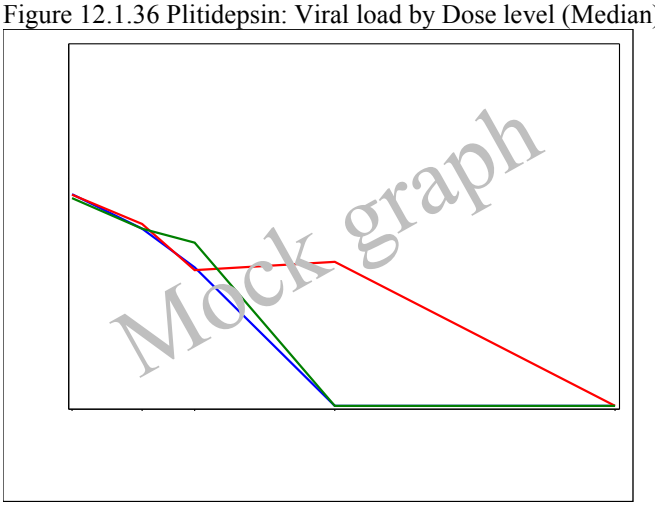
Two points improvement or discharged	Dose Cohort							
	1.5 mg N=X		2.0 mg N=X		2.5 mg N=X		Total N=X	
Day 7								
Day 15								
Day 31								

Table 12.1.35 FDA risk groups

	FDA risk groups at baseline			
	Mild	Moderate	Severe	p-value
Non-invasive mechanical ventilation, n (%)				
Yes				
No				
Invasive mechanical ventilation, n (%)				
Yes				
No				
High flow oxygen therapy, n (%)				
Yes				
No				
ICU admission, n (%)				
Yes				
No				
Days of hospital admission				
Days of symptom evolution				
CRP				
Ferritin				
AST				
ALT				
LDH				
Lymphocytes				

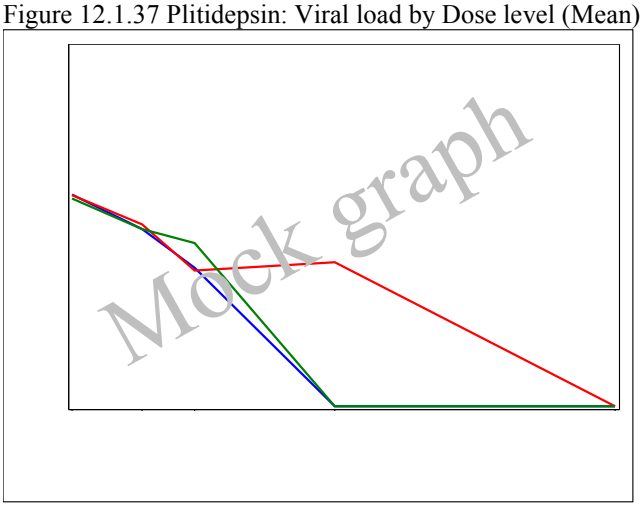
(*)It could be done by dose, if requested.

Figure 12.1.36 Plitidepsin: Viral load by Dose level (Median)



The lines represent the median value from baseline of the patients treated with viral load by central lab at the three dose levels in each time point(1.5mg n=x, 2.0 mg n=x, 2.5 mg n=x)

Figure 12.1.37 Plitidepsin: Viral load by Dose level (Mean)



The lines represent the mean value from baseline of the patients treated with viral load by central lab at the three dose levels in each time point (1.5mg n=x, 2.0 mg n=x, 2.5 mg n=x)

Figure 12.1.38 Plitidepsin: Viral load by FDA classification at baseline (Median)

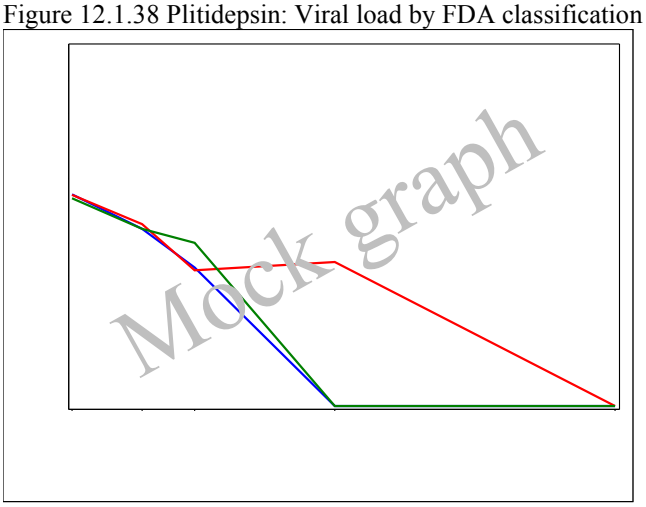


Figure 12.1.39 Plitidepsin: Viral load by FDA classification at baseline (Mean)

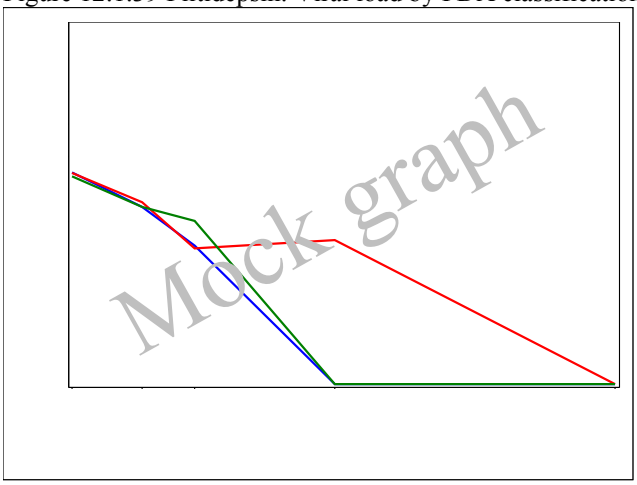


Figure 12.1.40 Plitidepsin: Viral load by Oxygen support on day 1 (Median)

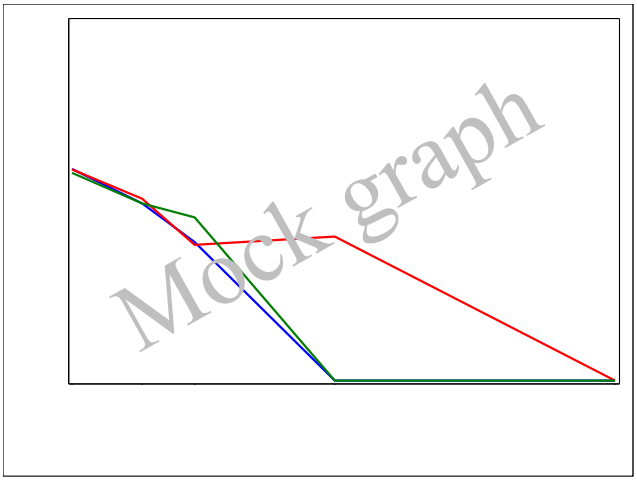


Figure 12.1.41 Plitidepsin: Viral load by Oxygen support on day 1 (Mean)

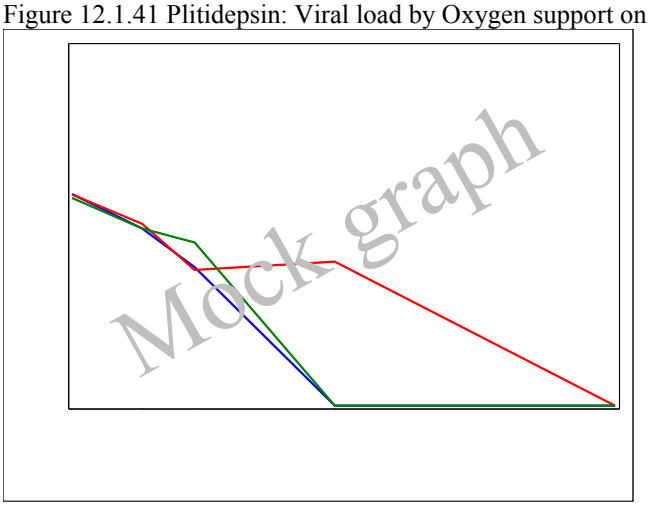
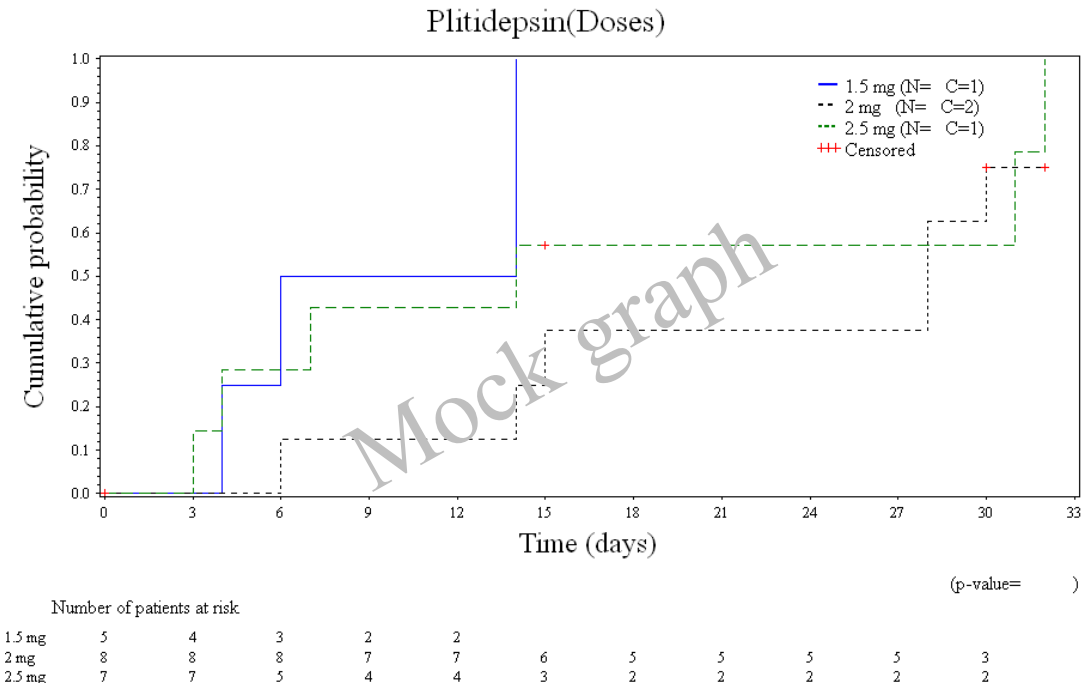


Figure 12.1.42 Time to negative detection of COVID-19 detection by PCR

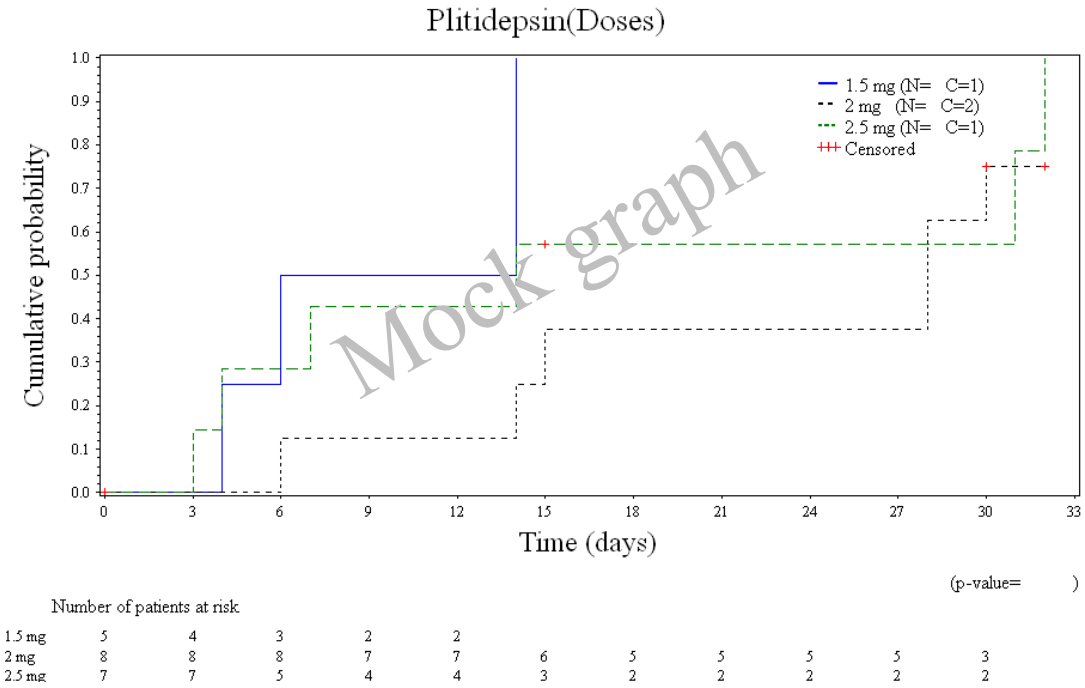


Number of patients at risk

1.5 mg	5	4	3	2	2						
2 mg	8	8	8	7	7	6	5	5	5	5	3
2.5 mg	7	7	5	4	4	3	2	2	2	2	2

(*) Table 12.1.37 will be also produced with median value and 95% confidence interval.

Figure 12.1.43 Time to Hospital discharge

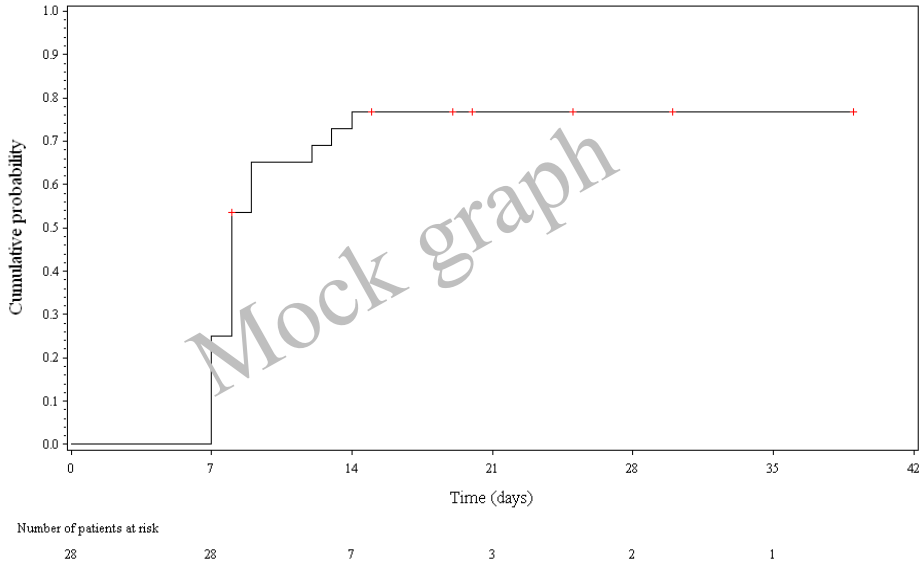


Number of patients at risk

1.5 mg	5	4	3	2	2						
2 mg	8	8	8	7	7	6	5	5	5	5	3
2.5 mg	7	7	5	4	4	3	2	2	2	2	2

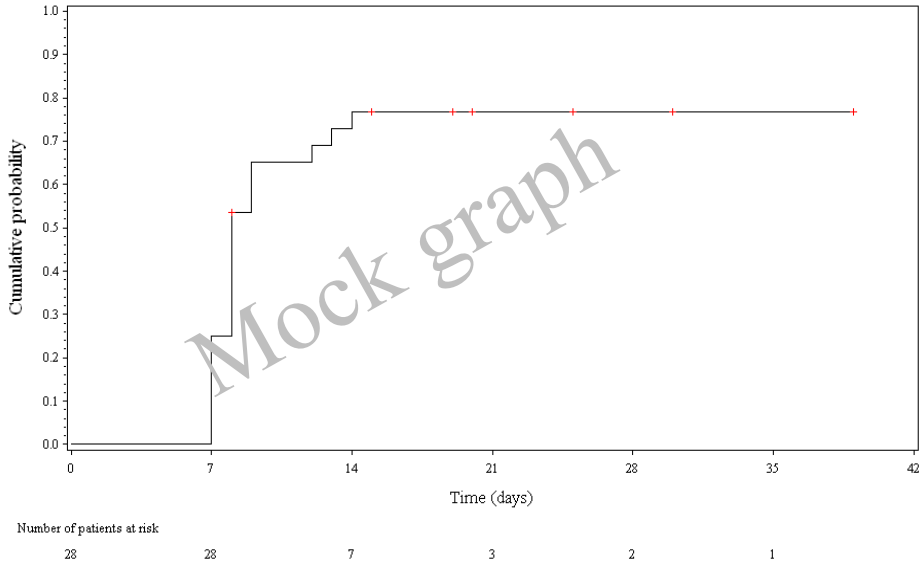
(*) Table 12.1.38 will be also produced with median value and 95% confidence interval.

Figure 12.1.44 Time to Hospital discharge – All patients



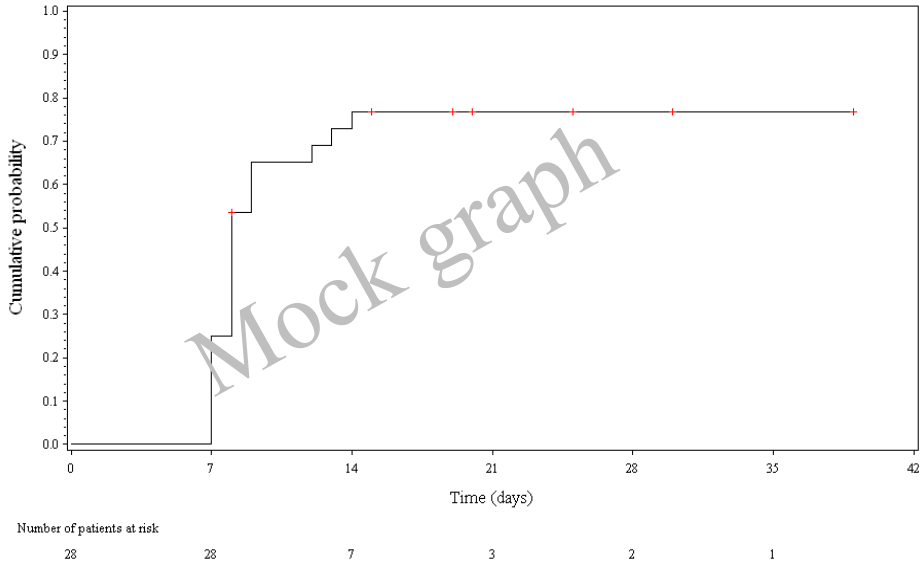
(*) Table 12.1.39 will be also produced with median value and 95% confidence interval.

Figure 12.1.45 Time to Hospital discharge by FDA classification



(*) Table 12.1.40 will be also produced with median value and 95% confidence interval.

Figure 12.1.46 Time to Hospital discharge by time from symptoms (<= 6 days vs >6 days



(*) Table 12.1.41 will be also produced with median value and 95% confidence interval.

Figure 12.1.47 Swimmer Plot of Hospital Discharge Day by Viral Load at Baseline

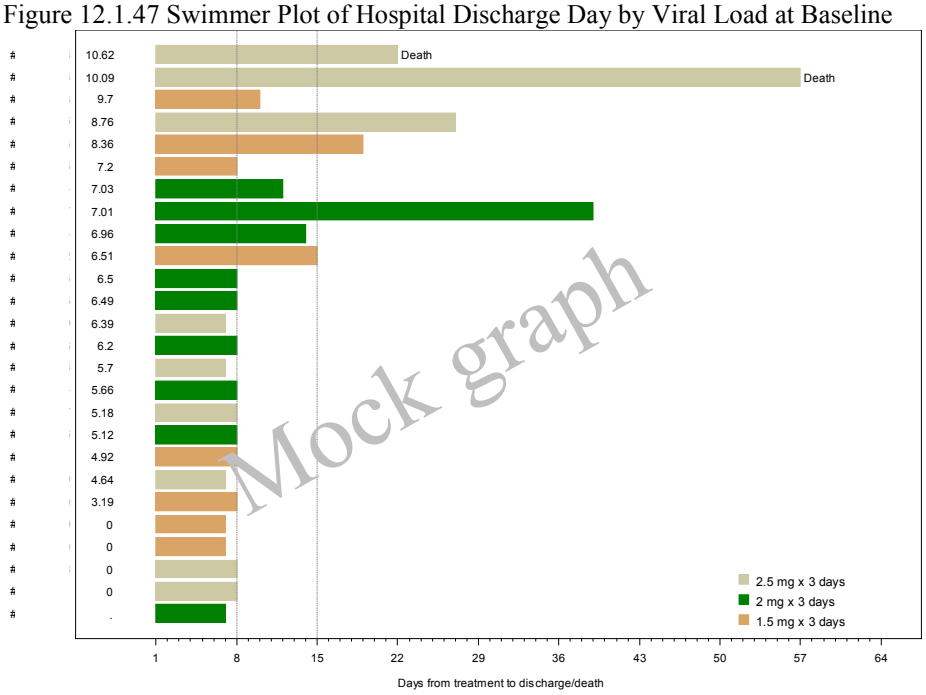


Figure 12.1.48 Swimmer Plot of Hospital Discharge Day by Disease Severity at Baseline

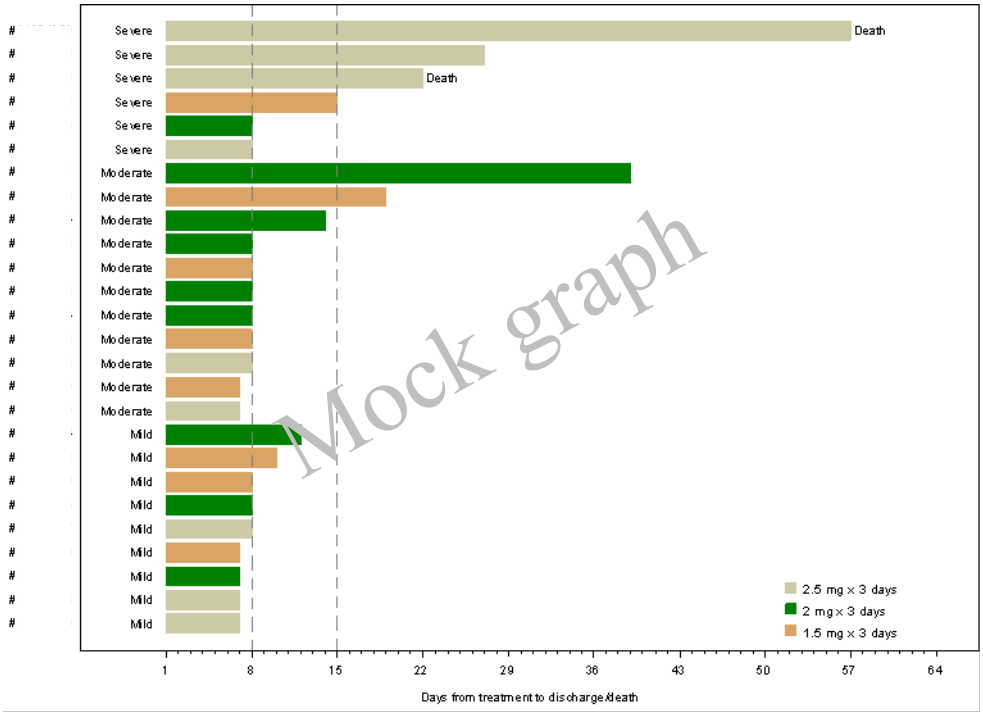


Figure 12.1.49 Swimmer Plot of Oxygen therapy

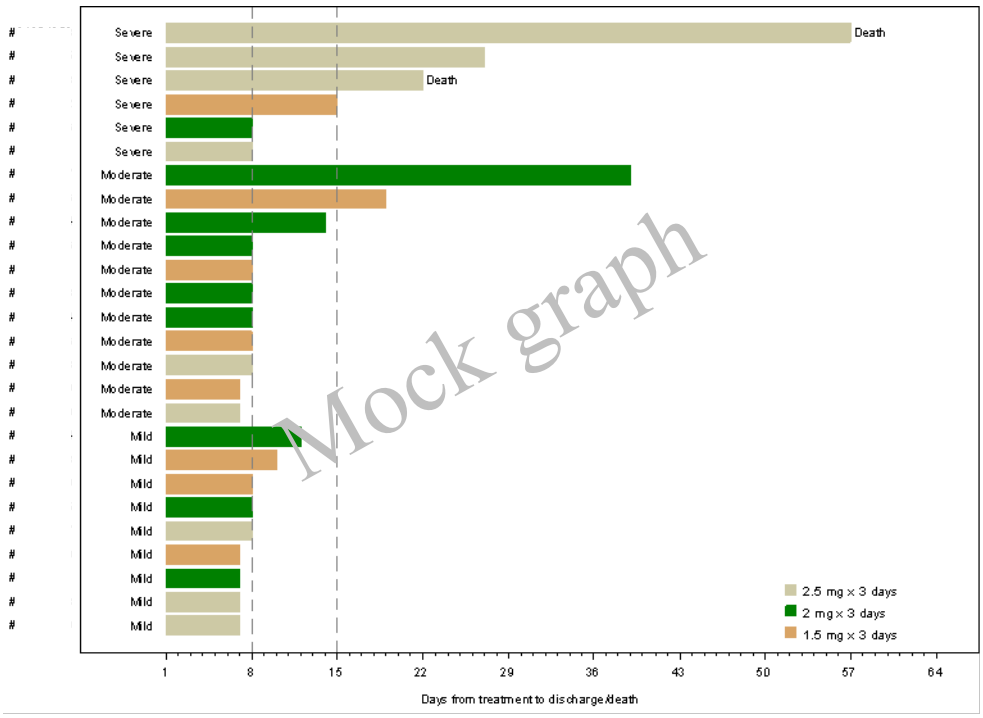


Figure 12.1.50 Viral load evolution per patient

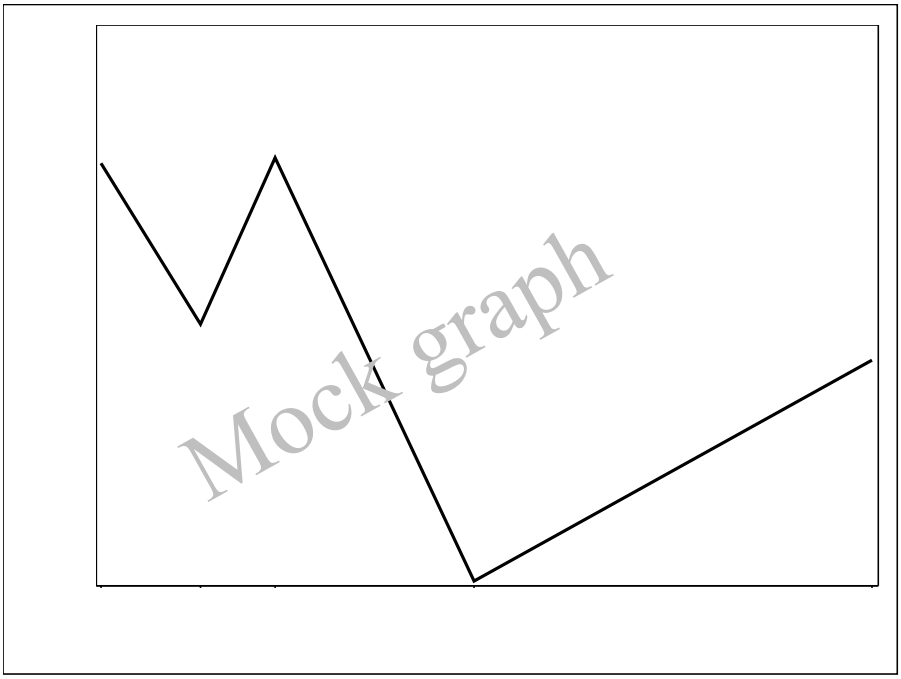


Figure 12.1.51 Viral load and C-reactive protein evolution per patient

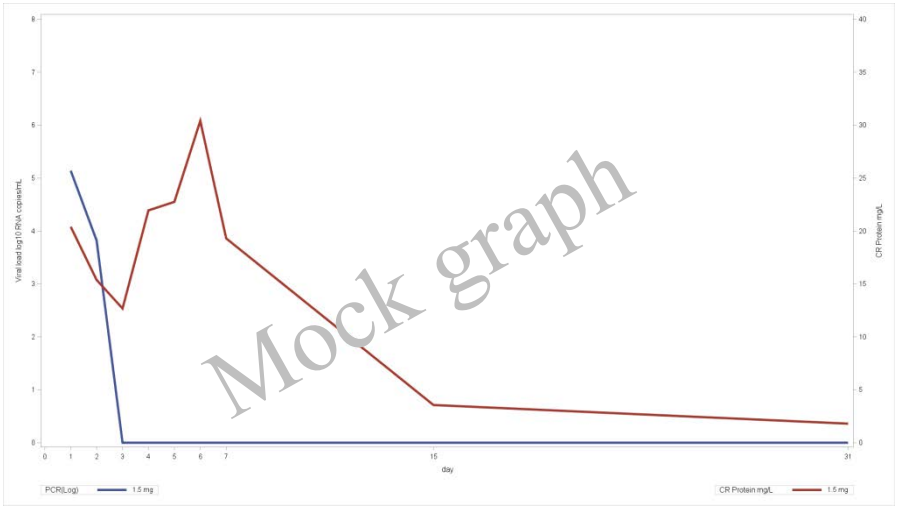


Figure 12.1.52 Viral load and C-reactive protein evolution by dose

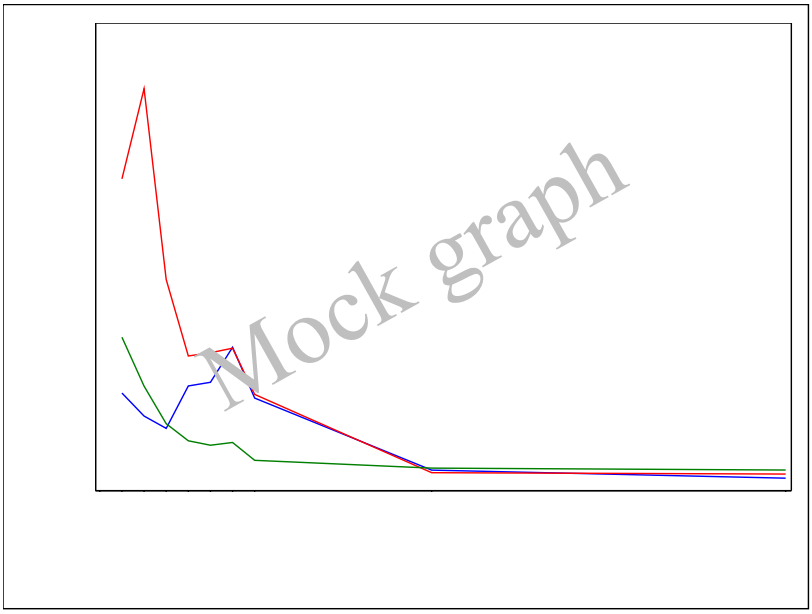


Figure 12.1.53 Viral load and C-reactive protein evolution by baseline level

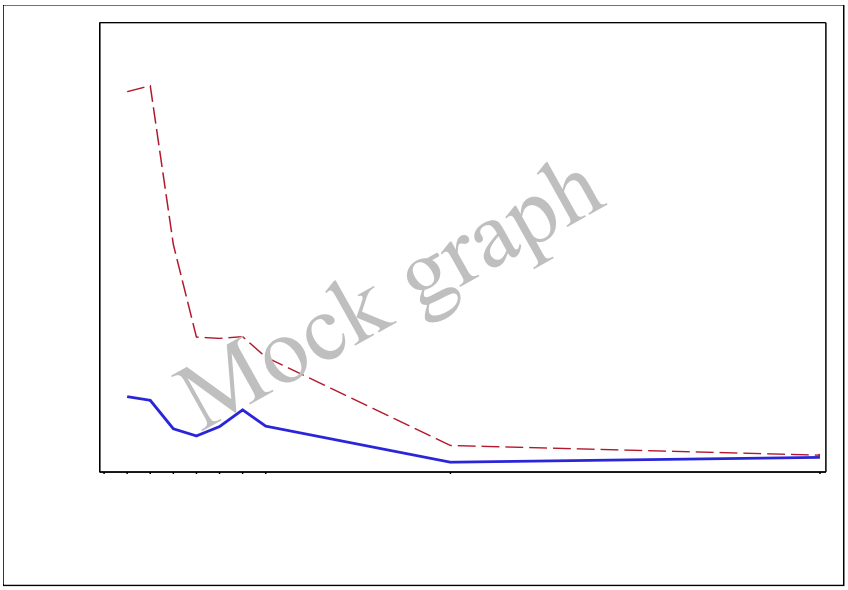


Figure 12.1.54 Viral load and LDH evolution per patient

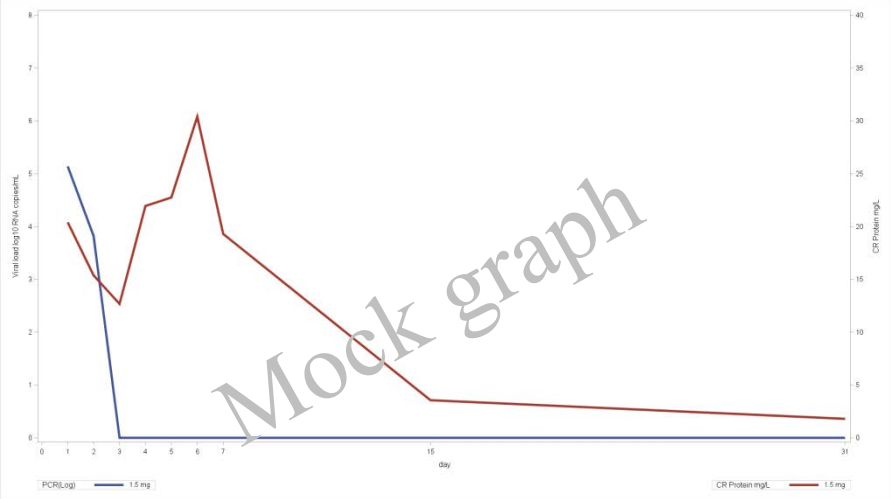


Figure 12.1.55 Viral load and LDH evolution by dose

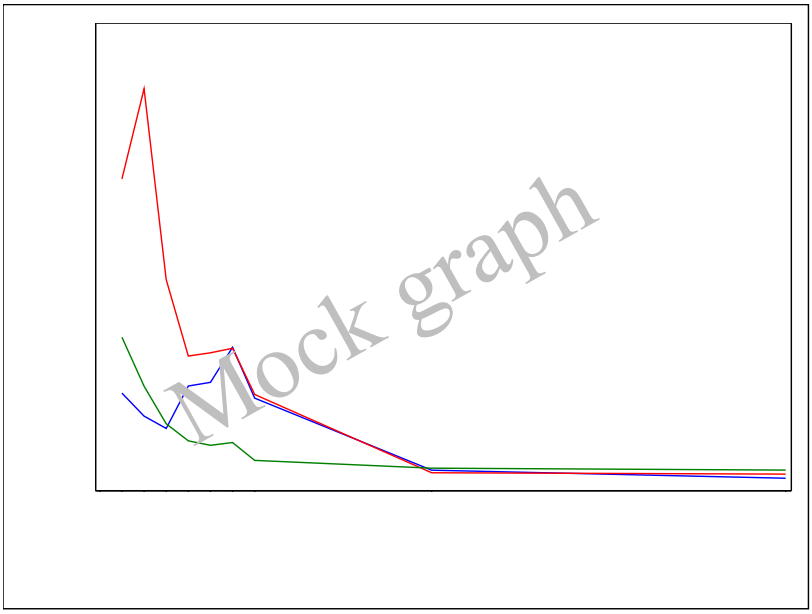


Figure 12.1.56 Viral load and LDH evolution by baseline level

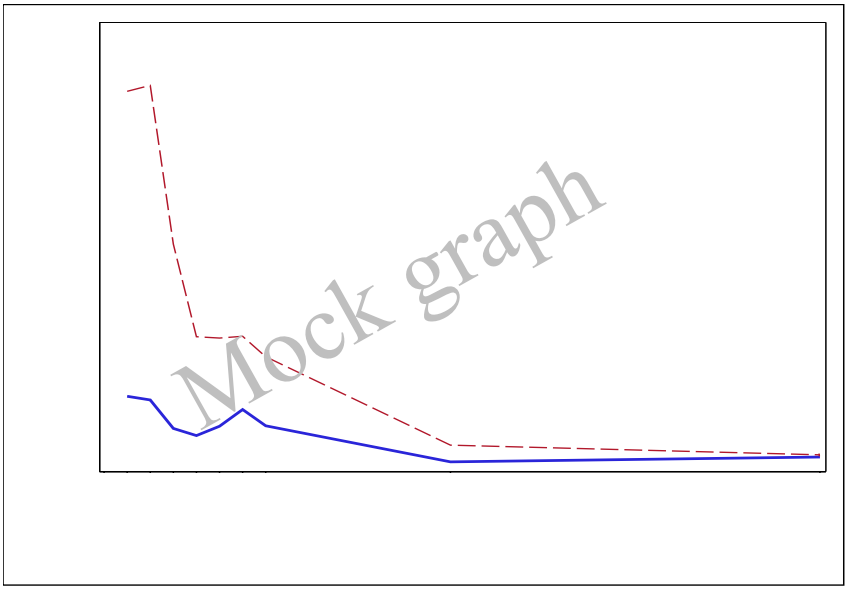


Figure 12.1.57 Viral load and Ferritin evolution per patient

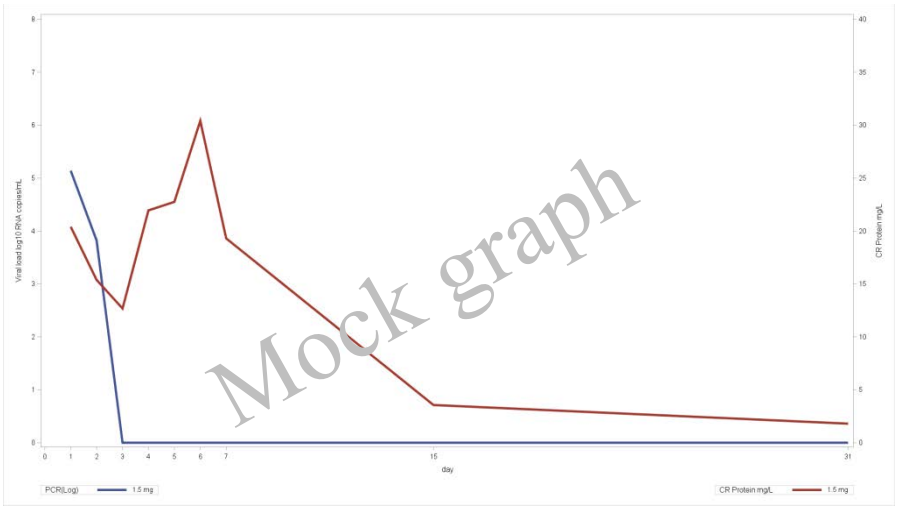


Figure 12.1.58 Viral load and Ferritin evolution by dose

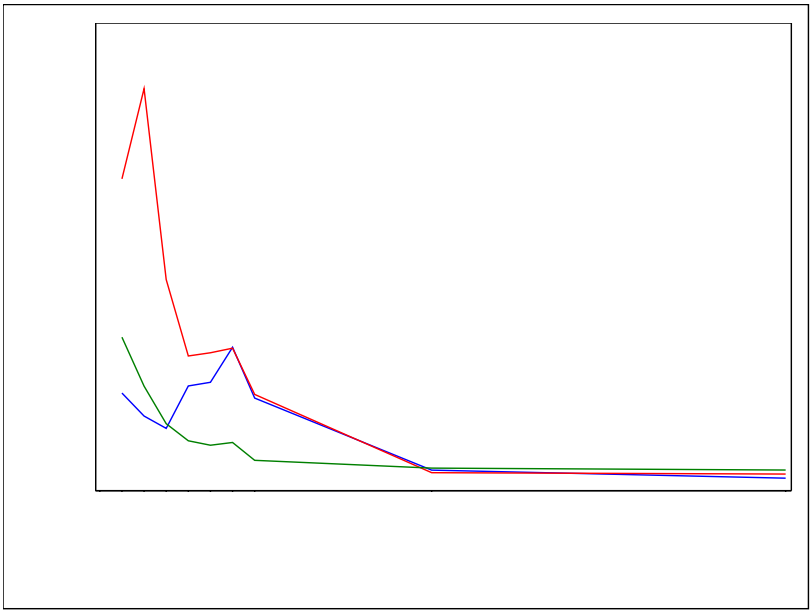


Figure 12.1.59 Viral load and Ferritin evolution by baseline level

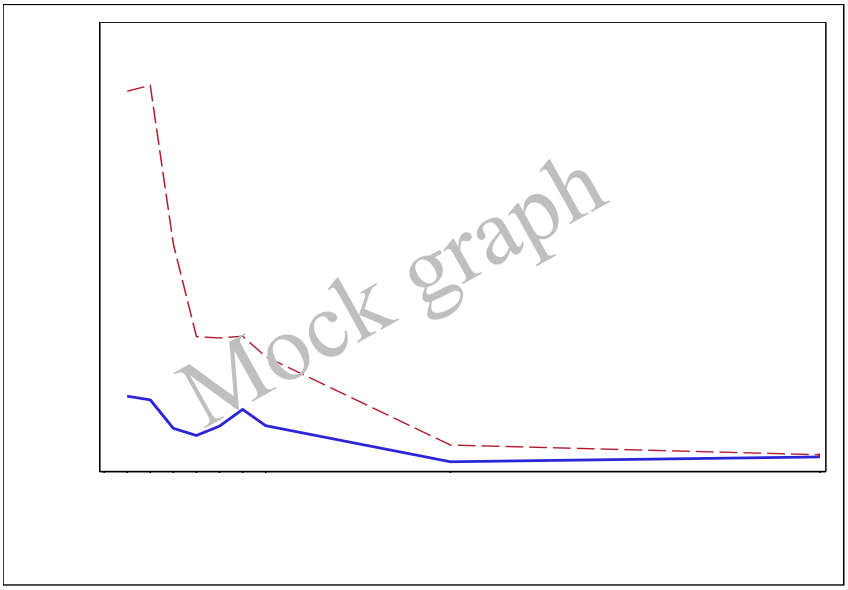


Figure 12.1.60 D-dimer median graph

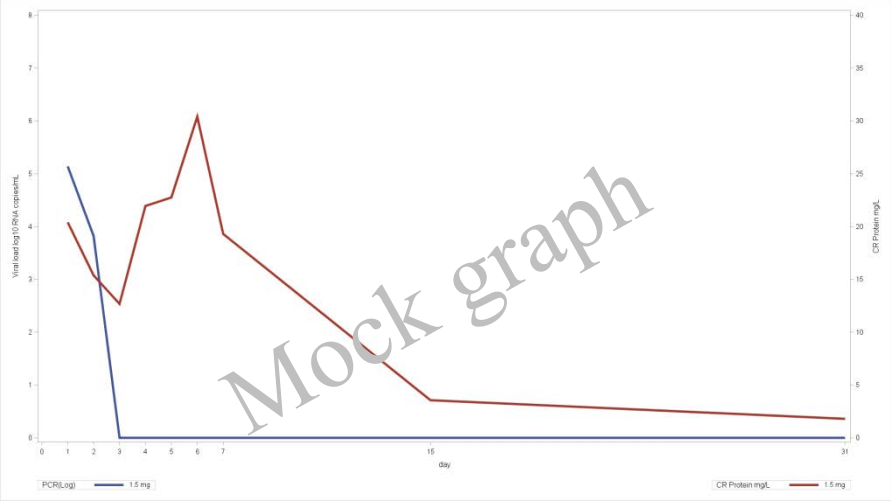


Figure 12.1.61 D-dimer evolution by dose

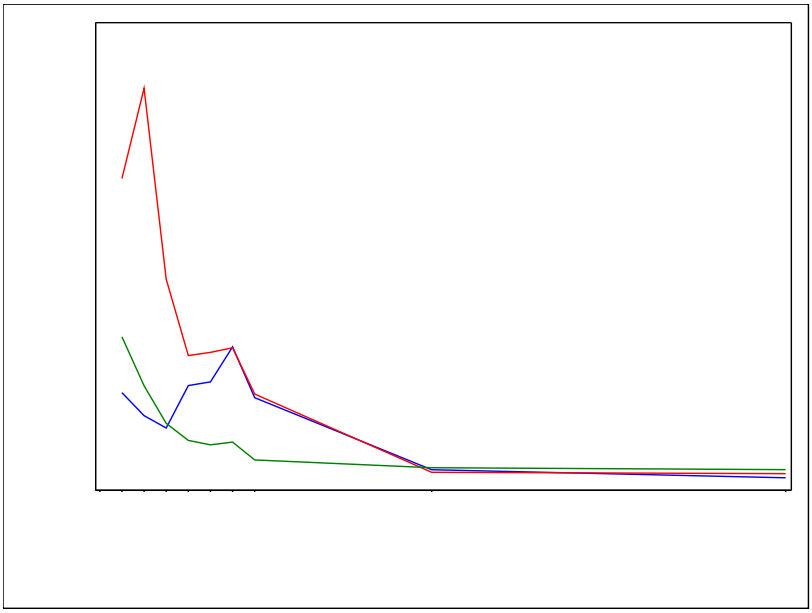


Figure 12.1.62 Viral load and D-dimer evolution by baseline level

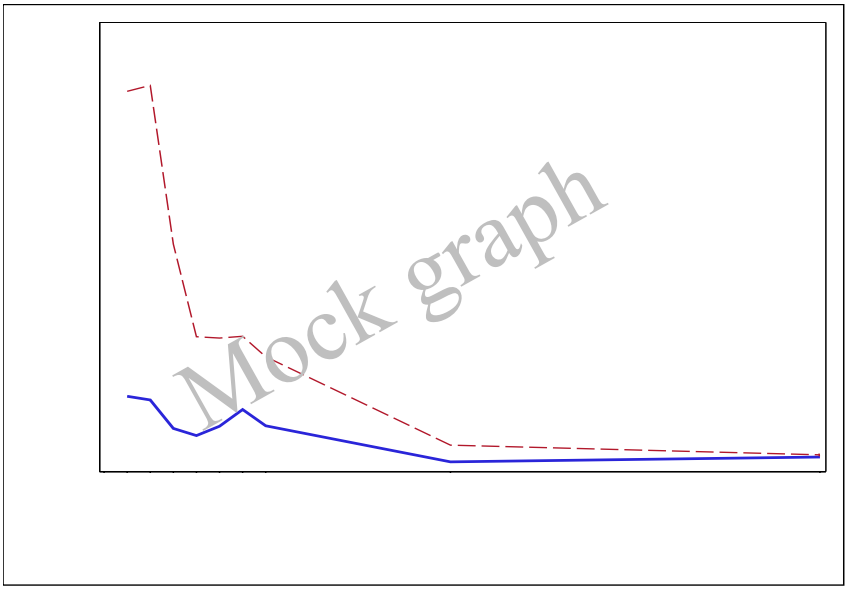


Figure 12.1.63 Viral load and Lymphocytes evolution per patient

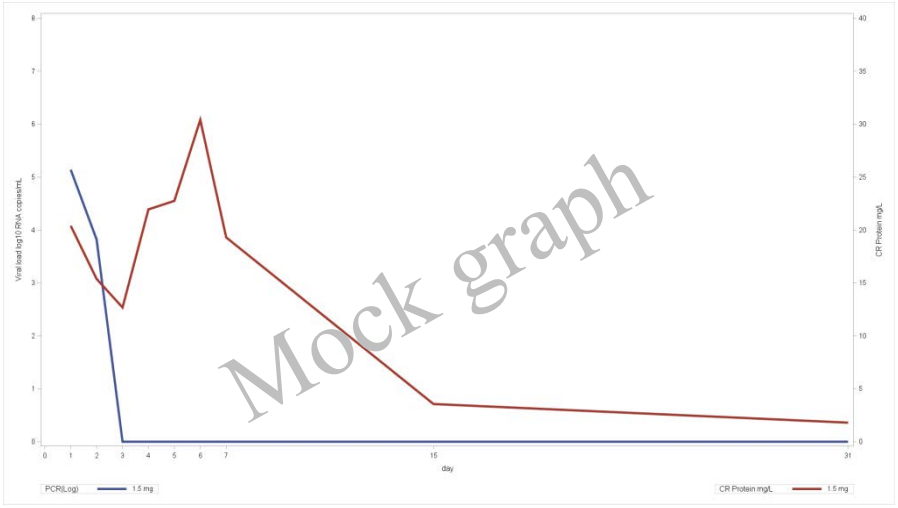


Figure 12.1.64 Viral load and Lymphocytes evolution by dose

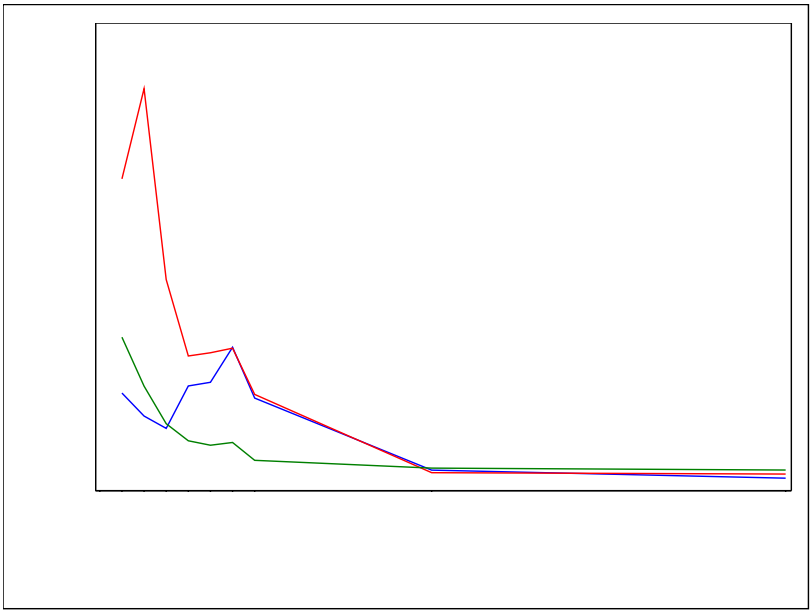


Figure 12.1.65 Viral load and Lymphocytes evolution by baseline level

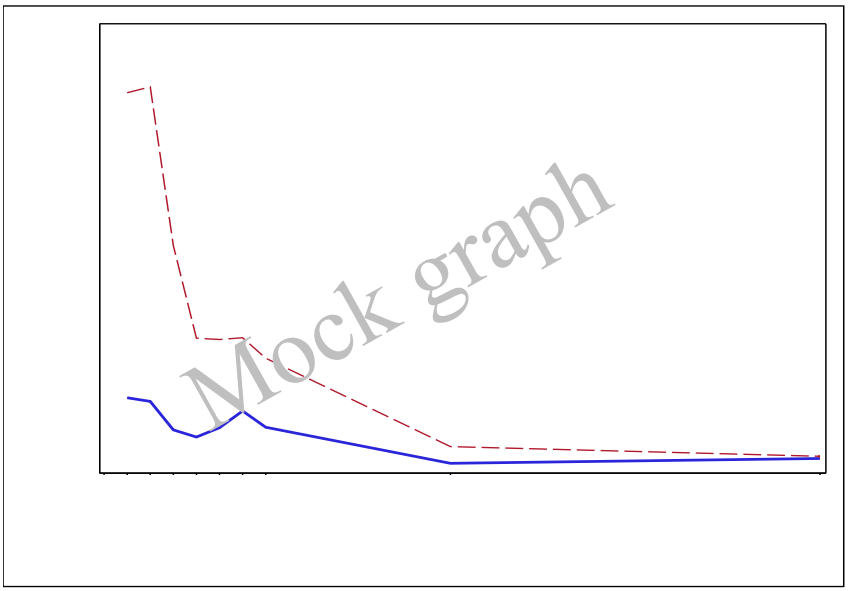


Figure 12.1.66 Six-point ordinal scale Heat map

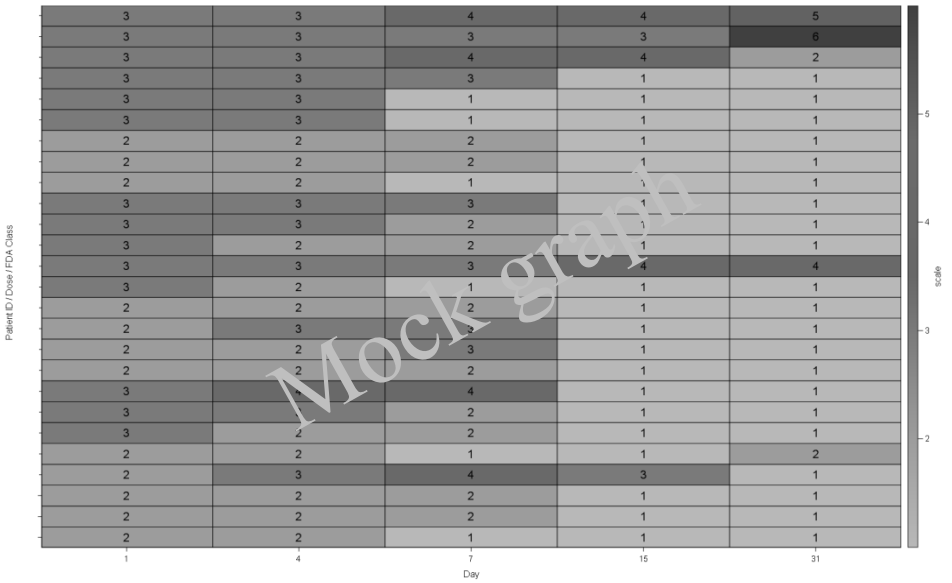
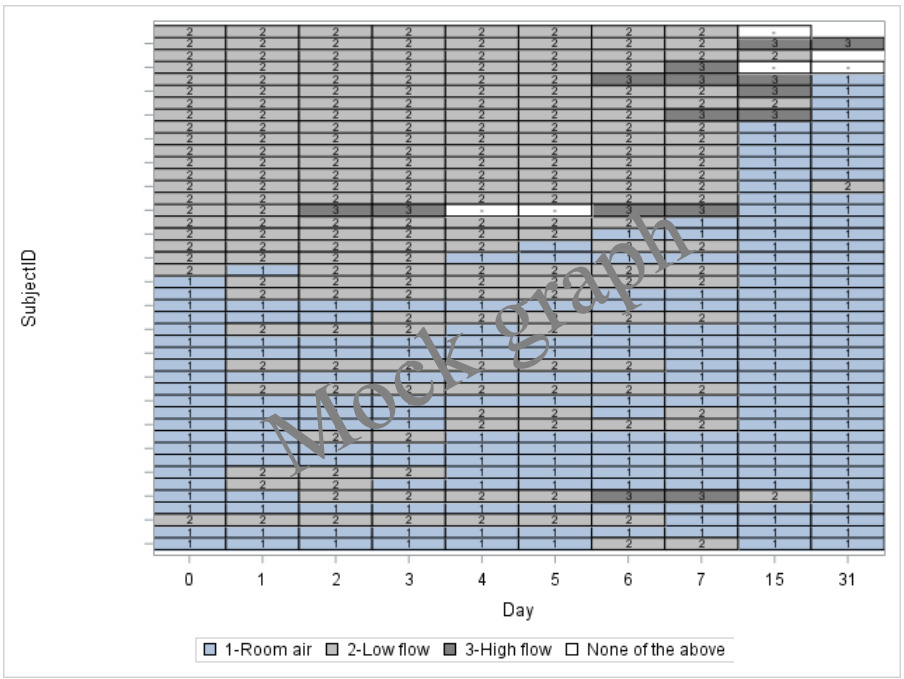


Figure 12.1.67 Oxygen therapy (Room air – Low flow – High flow- MV) heat map



APPENDIX IV

13 LISTINGS

The following listings will be done according to listings described in SAP section 9.

Listing 13.1 Demographics, symptoms, and comorbidities data. Demographics (I)

Arm	Center	Patient id.	Dose (mg)	Age	Gender	Ethnic	Days from onset of 1st symptom to hospital admission	Days from onset of 1st symptom to 1st plitidepsin dose	Days from hospital admission to 1st plitidepsin dose
…	…..								

Listing 13.1 Demographics, symptoms, and comorbidities data. Comorbidities (II)

Arm	Center	Patient id.	Dose (mg)	Fever	Dehydration	cough	….
…	…..						

Sputum production, Hemoptysis, Runny nose, Earache, Crackles, Thoracic Pain, Muscular pain, Joint pain, Fatigue, Short of breathe, Intercostal retraction, Headache.

Listing 13.1 Demographics, symptoms, and comorbidities data. Comorbidities (III)

Arm	Center	Patient id.	Dose (mg)	Confusion	Convulsion	Nausea	….
…	…..						

Abdominal pain, Diarrhea, Conjunctivitis, Rash, Skin ulcer, Lymphadenopathy, Throat pain, Bleeding, Bleeding location.

Listing 13.1 Demographics, symptoms, and comorbidities data. Comorbidities (**IV**)

Arm	Center	Patient id.	Dose (mg)	Cardiac pathologies	Arterial Hypertension	Asthma	….
…	…..						

Chronic lung disease, Diabetes with complications, Diabetes without complications, Chronic kidney disease, Rheumatic disorder, Moderate or severe liver disease, Mild liver disease, Dementia.

Listing 13.1 Demographics, symptoms, and comorbidities data. Comorbidities (**V**)

Arm	Center	Patient id.	Dose (mg)	Malnutrition	Chronic neurological disorder	Smoker	….
…	…..						

Smoker, Malignant neoplasm, Chronic hematological disease, AIDS, obesity, Other risk factors, Specify risk.

Listing 13.1 Demographics, symptoms, and comorbidities data. Symptoms (VI)

Arm	Center	Patient id.	SBP mmHg	DBP mmHg	Heart rate	Respiratory rate	Temperature Cº	Saturation O2 %	Saturation measures	Oxygen therapy	Flow L/min	FiO2 (%)	PaO2 mmHg	PaO2/FiO2
…	…										.	.	.	.

Listing 13.1 Demographics, symptoms, and comorbidities data. Electrocardiogram and X-ray results (VII)

Arm	Center	Patient id.	Chest X-ray	X-ray result	X-ray abnormalitiy	X-ray Other	ECG	ECG result	ECG abnormality	ECG QT interval	ECG PR interval	ECG Other
…	…											

Listing 13.2 Screening failures

Arm	Center	Patient id.	Dose (mg)	Screening failure reason
…	…..			

Listing 13.3 Treatment data. Treatment (I)

Arm	Center	Subject id.	Treatment administration	Reasons	Dose (mg)	Treatment Interruption	Reasons	Pre-medication	…

Days on treatment, total dose, End of treatment date; Reason

Listing 13.3 Treatment data. Pre-medication (II)

Subject id.	Visit	Type	Code (ATC)	Active substance	Dose	Units	Route

Listing 13.4 Adverse events

Arm	Center	Subject id.	Age	Number of AE	Original term	System (SOC)	Prefered term (PT)	Grade

Seriousness, Start date, Ongoing, End date, Actions taken, Relationship, Specify, Outcome, Severity criteria, Onset day, Nausea/Vomiting at baseline, prophylactic medication Yes/No.

Listing 13.5 Laboratory parameters. Hematological (I)

Arm	Center	Subject id.	Visit	Date	Basophils (10^9/L)	Basophils Change(%)	Eosinophils (10^9/L)	Eosinophils change (%)	Erythrocytes (10^12/L)	Erythrocytes change (%)

Hematocrit, Hemoglobin, Platelets, Leukocytes, Neutrophils, Lymphocytes, Lymphocytes-neutrophils, Monocytes.

Listing 13.5 Laboratory parameters. Coagulation (II)

Arm	Center	Subject id.	Visit	Date	APTT	APTT change (%)	PT	PT change (%)	D-dimer	D-dimer change (%)	INR	INR change (%)

Listing 13.5 Laboratory parameters. Biochemical (III)

Arm	Center	Subject id.	Visit	Date	ALP IU/L	ALP change %	BIL mg/dL	BIL change %	CPK IU/L	CPK change %	Creatinine mg/dL	Creatinine change %	CRP mg/L	CRP change%

Glucose, ALT, AST, GGT, LDH, Troponin, Ferritin

Listing 13.6 Other COVID-19 treatment (I)

Arm	Center	Subject id.	Other covid treatment	Clorine/ hydroxychloroquine	Tocilizumab	Remdesivir	Lopinavirritonavir	IFN B 1B

Other, other specify:

Listing 13.6 Other COVID-19 treatment . Support treatment (II)

Arm	Center	Subject id.	Antibiotic	AzitromizinA	Other Antibiotic	Other Antibiotic:	Antifungal Agents	Other support treatment

Listing 13.6 Other COVID-19 treatment Corticosteroids (III)

Arm	Center	Subject id.	Corticosteroids	Corticosteroids Onset day	Corticosteroids Duration (days)	Corticosteroid total daily dose

Listing 13.7 Concomitant medication or procedures

Arm	Center	Subject id.	Medication / Procedure	Description	Use	Active substance	Code (ATC)	Start date	Ongoing	End date	Dose	Units

Frequency, Route, Indication, Specify.

Listing 13.8 End of study

Arm	Center	Subject id.	End of Study	Reason	End of study date	Follow-up time

Listing 13.9 Deaths

Arm	Center	Subject id.	End of treatment	Cause of death	Specify	Adverse event	Grade	Relationship

Listing 13.10 Protocol deviations

Arm	Center	Subject id.	Deviation date	Category	Deviation type	Reason (text)

14 ICH LISTINGS

Following ICH E-3 guideline, patient listings will be performed.

- 16.2.1 Discontinued Patients
- 16.2.2 Protocol Deviations
- 16.2.3 Patients Not Included in the Efficacy Analysis
- 16.2.4 Demographic Data
- 16.2.5 Compliance and/or Drug Concentration Data
- 16.2.6 Individual Efficacy Response Data
- 16.2.7 Adverse Event Listing (each patient)
- 16.2.8 Listing of Individual Laboratory Measurements by Patient

APPENDIX V

15 Additional figures with R software

Some additional descriptive figures performed with R are added as supportive analyses.

An outcome classification (good or poor) will be used to compare in this section these subgroups.

This classification will be calculated as follow:

- Good outcome: Patients alive and Discharged before day 9
- Poor outcome: Patients death or not discharge before day 9

15.1 Overall Outcomes Discharge

Figure 15.1.1 Time to discharge per dose / FDA category

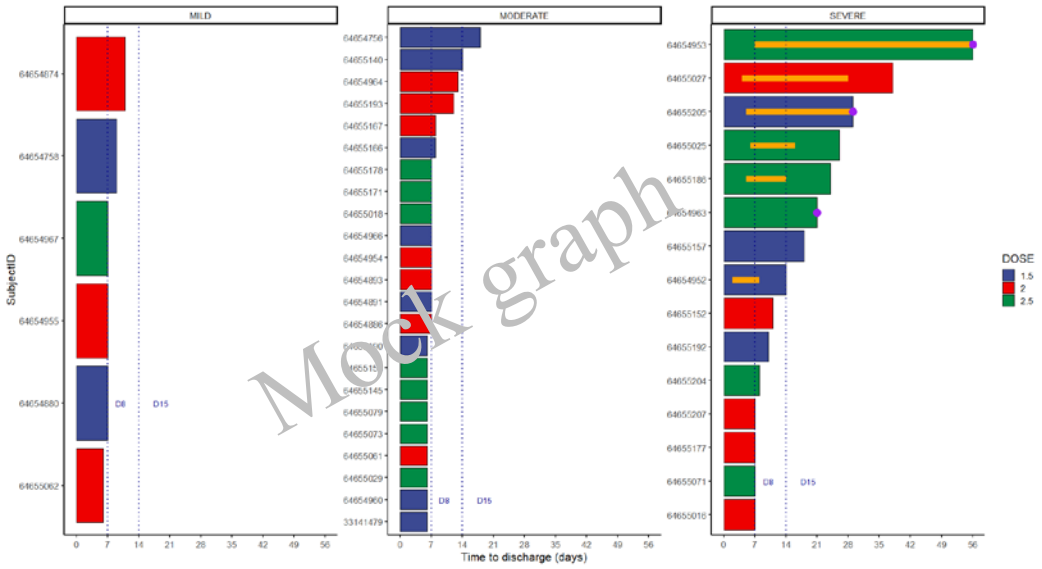


Figure 15.1.2 Probability of discharge per FDA category

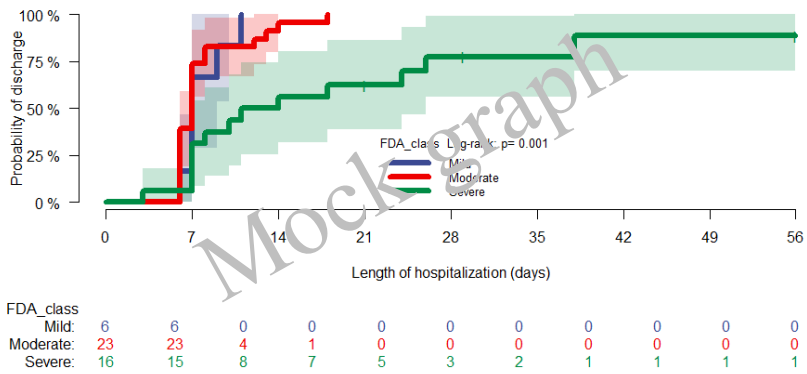


Figure 15.1.3 Time to discharge per dose level (Moderate patients)

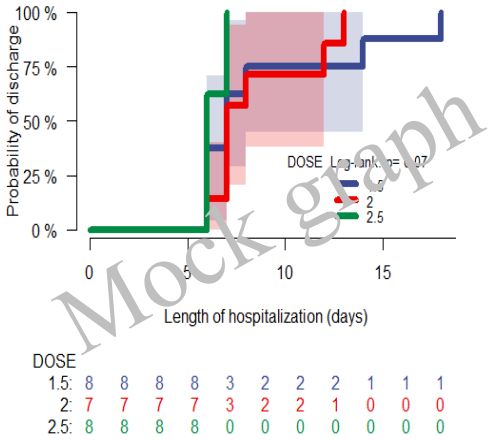
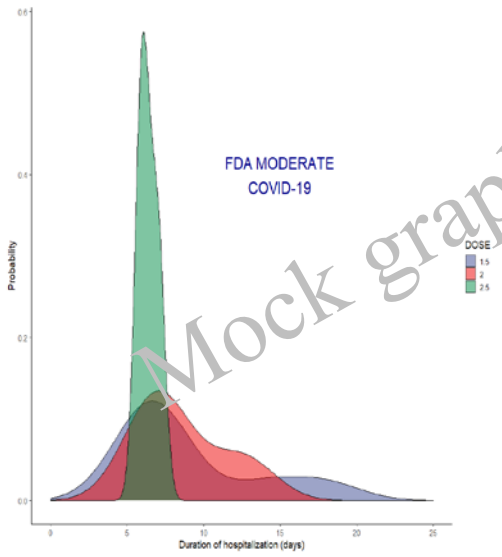


Figure 15.1.4 Duration of Hospitalization (Moderate patients)



15.2 Outcomes Kinetics

Figure 15.2.1 Viral load evolution by Outcome patient profile (Good vs poor)

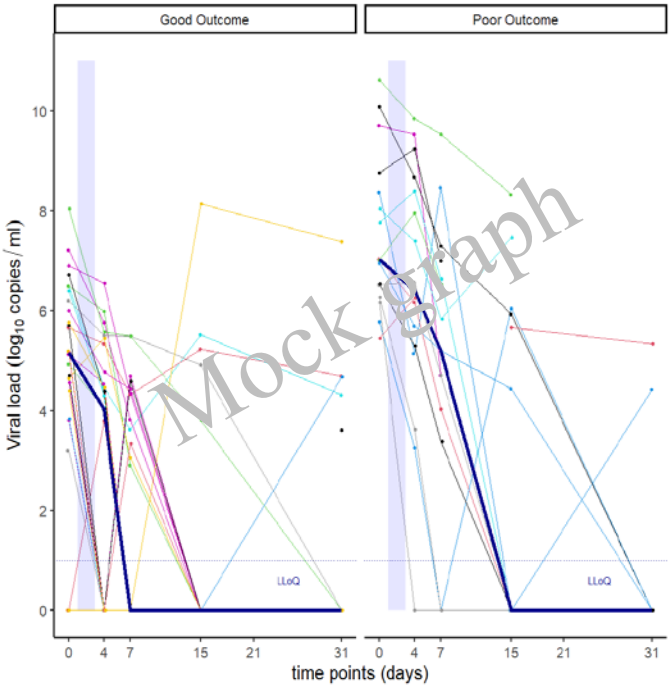


Figure 15.2.2 Viral load evolution (mean) by Outcome patient profile (Good vs poor)

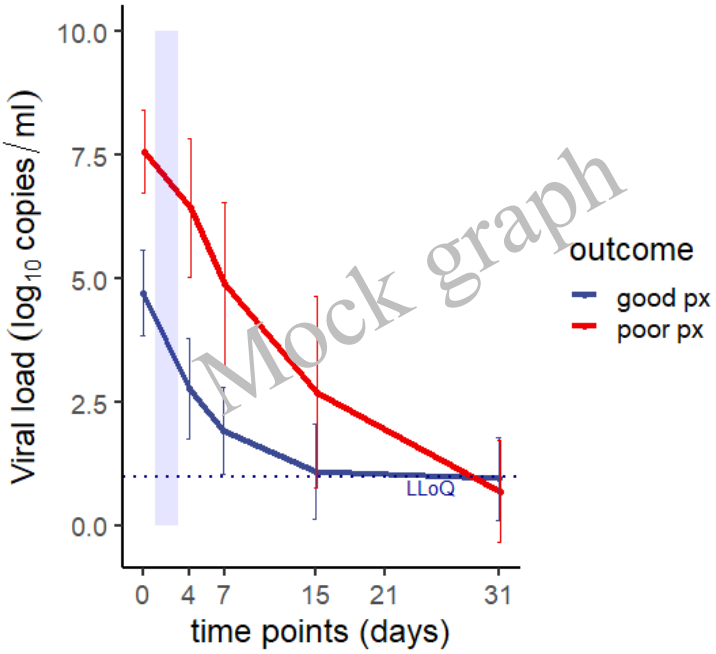


Figure 15.2.3 Viral load evolution (Plitidepsin vs control vs Remdesivir)

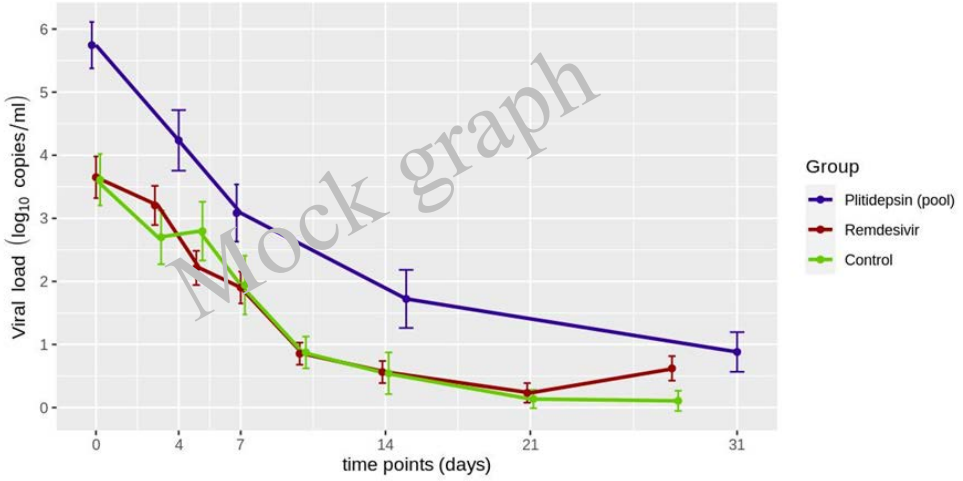
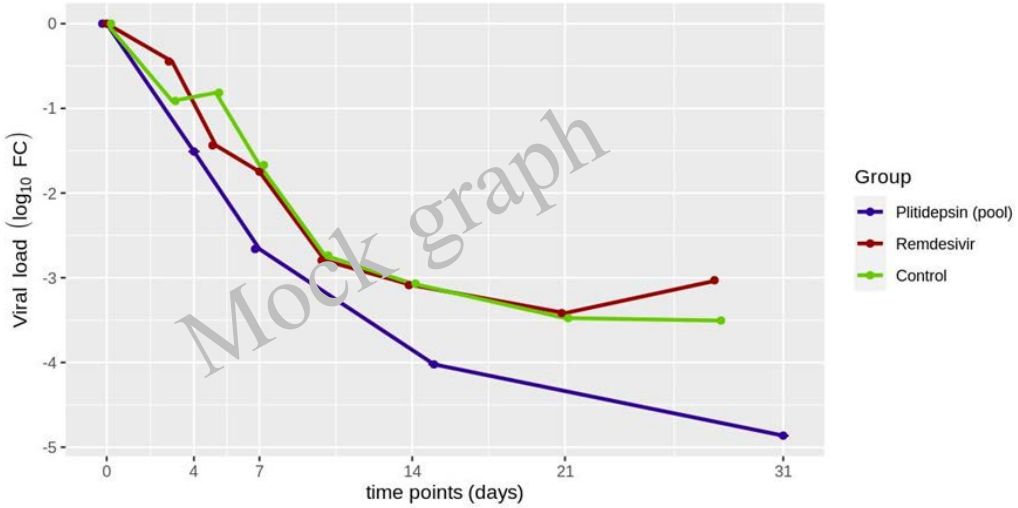


Figure 15.2.4 Viral load evolution Fold Change (Plitidepsin vs control vs Remdesivir)



15.3 Outcomes Inflammation Markers

Figure 15.3.1 Viral load evolution (mean) by FDA classification

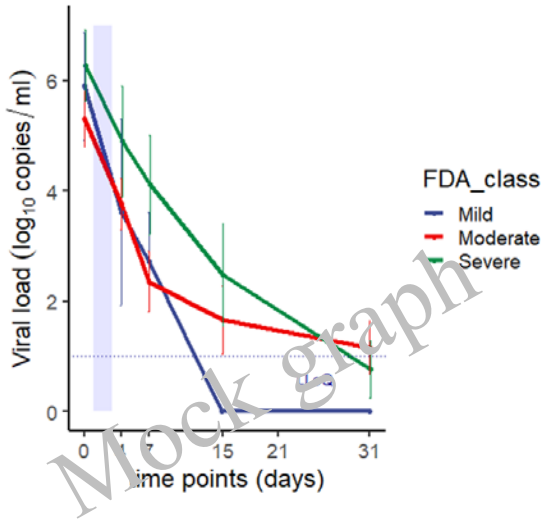


Figure 15.3.2 Viral load evolution (mean) Moderate patients (FDA classification) by dose

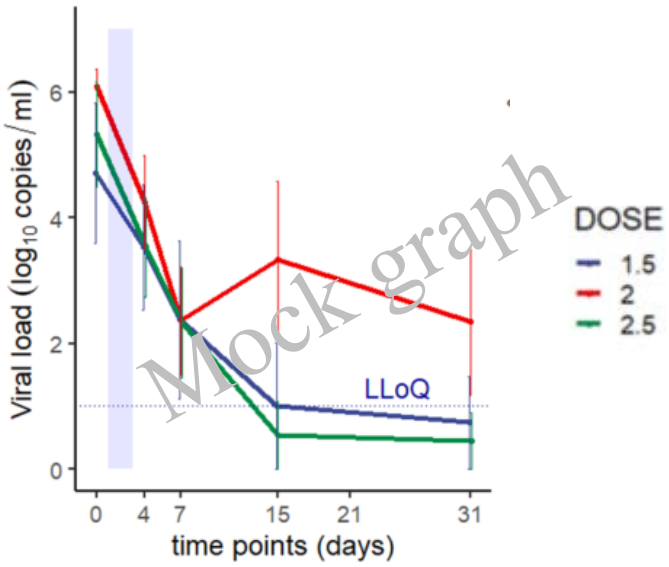


Figure 15.3.3 Lymphocytes evolution (mean) by dose (Moderate patients)

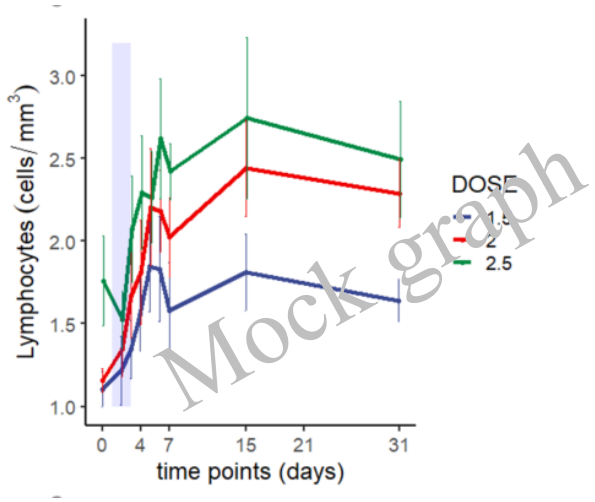


Figure 15.3.4 C-reactive protein evolution (mean) by FDA classification
Figure 15.3.5 Neutrophils/Lymphocytes evolution (mean) by FDA classification
Figure 15.3.6 D-dimer (mean) by FDA classification

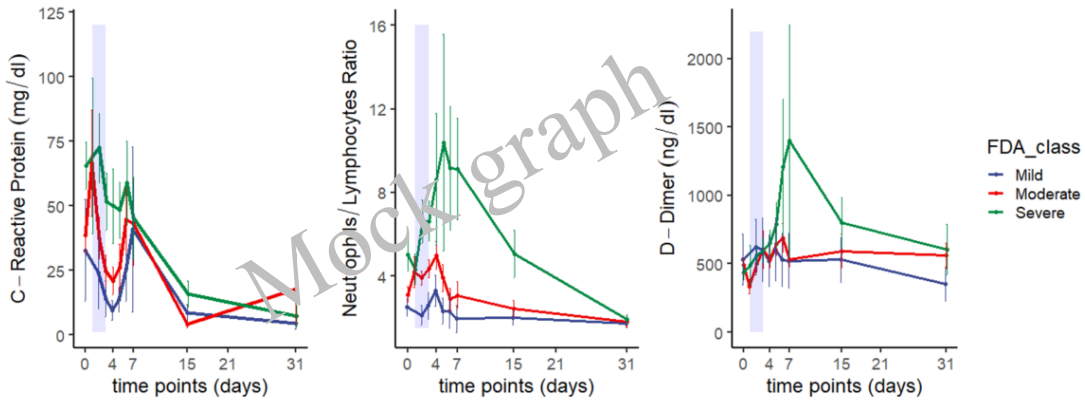


Figure 15.3.7 C-reactive protein evolution (mean) by dose (Moderate patients)
Figure 15.3.8 Neutrophils/Lymphocytes evolution (mean) by dose (Moderate patients)
Figure 15.3.9 D-dimer (mean) by dose (Moderate patients)

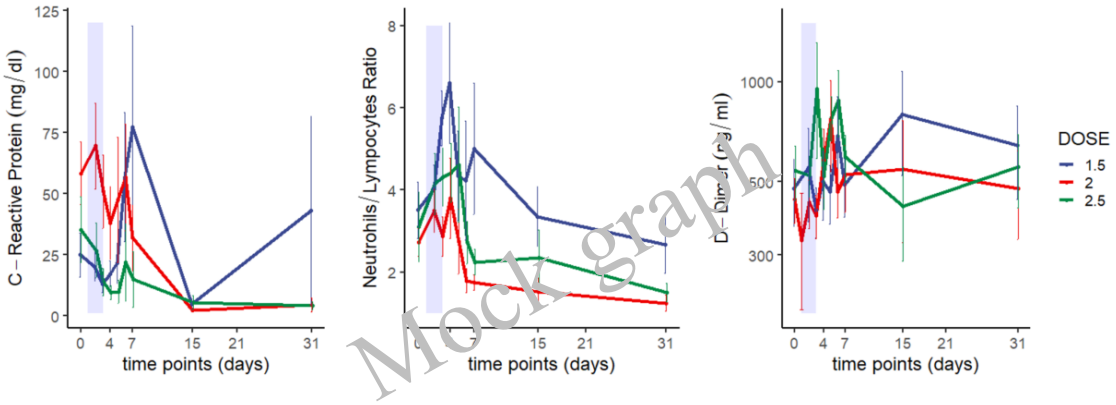


Figure 15.3.10 Intrapatient time-variation of Neutrophil/Lymphocyte ratio (NLR), per dose cohort, and median trends

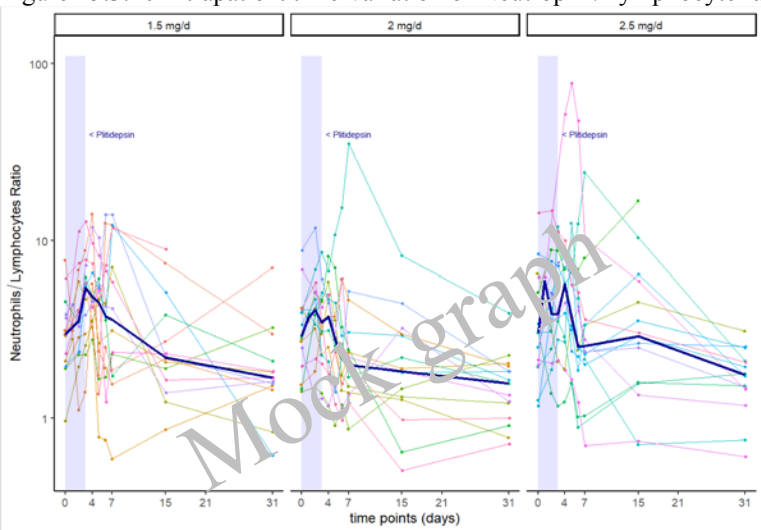


Figure 15.3.11 Intrapatient C-Reactive protein time variation, per dose cohort, and median trends

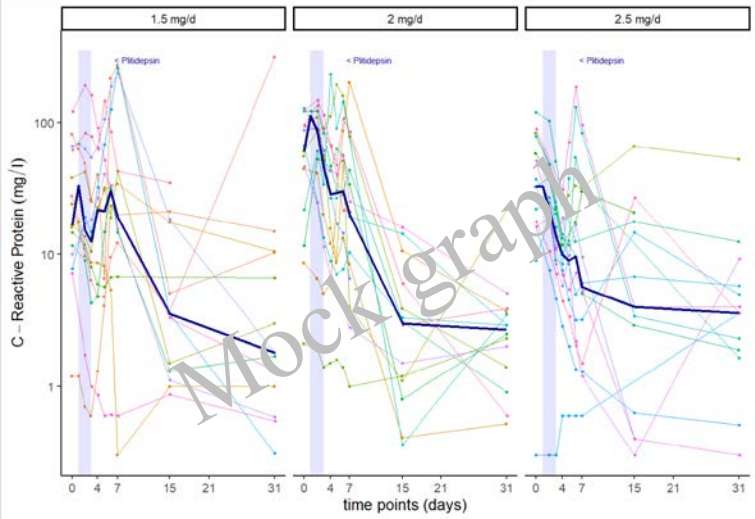


Figure 15.3.12 Intra-patient time-variation in ALT (normalized values), per dose cohort, and median trends (ULN: Upper Limit of Normality)

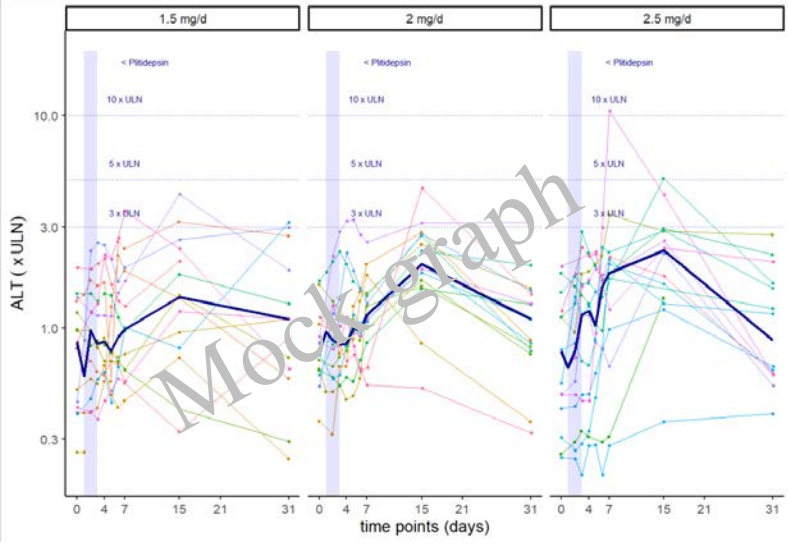
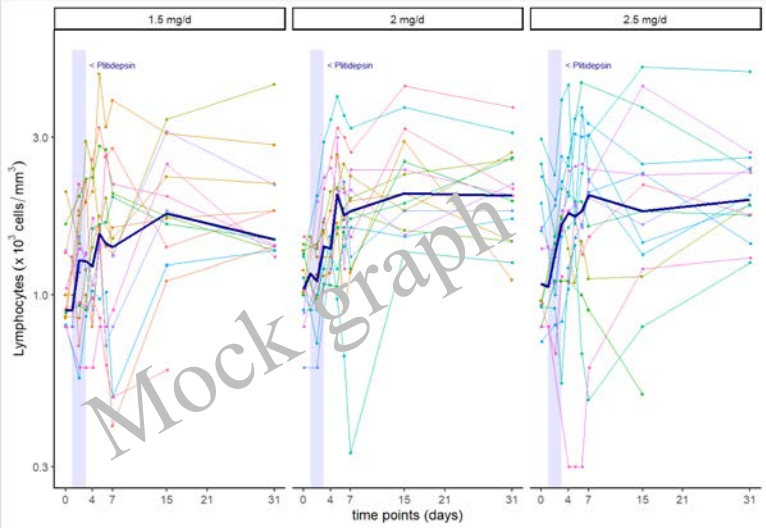


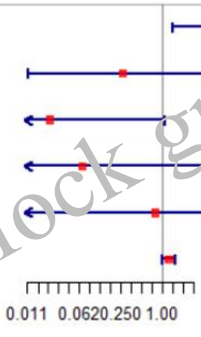
Figure 15.3.13 Intra-patient time-variation in lymphocyte count, per dose cohort, and median trends.



15.4 Regression Model.

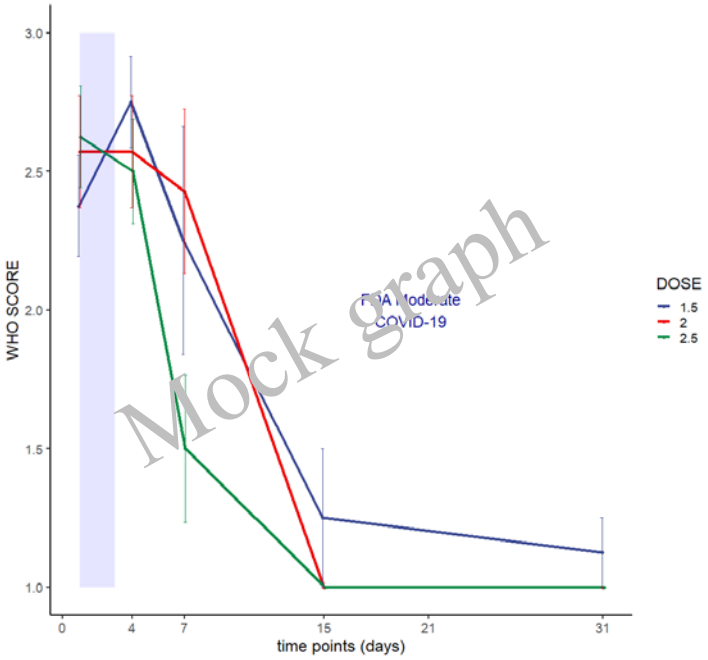
Figure 15.4.1 Logistic regression model – Discharge at D8

variable	OR	Regression Estimate	p-value
Baseline viral load	11.482	2.4408	0.0224
Dose: 2 mg/d vs 1.5 mg/d	0.268	-1.3169	0.4165
Dose: 2.5 mg/d vs 1.5 mg/d	0.0233	-3.7592	0.0561
FDA Moderate vs Mild	0.0687	-2.6784	0.2528
FDA Severe vs Mild	0.7775	-0.2517	0.9151
Age (continuous)	1.238	0.2135	0.0526



15.5 Outcomes Ordinal Scale

Figure 15.5.1 Evolution of Clinical Performance (6-category scale) in APLICOV Patients with FDA-Moderate COVID-19.



APPENDIX VI

The categorization of the disease severity in APLICOV-PC patients was performed following FDA Guidance (1).

All patients included in APLICOV-PC had non-invasive oximetry evaluations performed at baseline. For some of them, oximetry was not assessed at room-air conditions, what implies that these patients were receiving oxygen supplementation. Consequently, their disease severity was categorized at least 'Moderate' in the FDA classification. To discriminate between 'Moderate' and 'Severe' categories, according to FDA guidance, we evaluated PaO2/FiO2 ratio, among other variables.

As these patients only had determinations of oxyhemoglobin percent saturation with a pulse oximeter (SpO2), we needed to implement a method for the estimation of the PaO2/FiO2 ratio to evaluate disease severity. The SpO2/FiO2 ratio has been proposed as a noninvasive surrogate for the PaO2/FiO2 ratio. (2-7) To ensure equivalence, a noninvasive surrogate would require imputation of PaO2 from SpO2.

The relationship between PaO2 and SpO2 is sigmoidal. However, prior work investigating the association between SpO2/FiO2 and PaO2/FiO2 ratios employed linear (or log-linear) regression modeling in adults (2, 3) and children. (4-7)

The Ellis inversion (8) (Figure 1) of the Severinghaus equation (9) provides a useful nonlinear method for imputing PaO2 from SaO2. This technique has been used in cohorts of mostly nonintubated patients with pneumonia. (10-12)

In a recent work exploring different methods, the nonlinearly imputed PaO2/FiO2 based on the Severinghaus equation outperformed linear and log-linear imputations for PaO2/FiO2. In addition, the mortality associated with non-linearly imputed PaO2/FiO2 thresholds was closer to the mortality associated with measured PaO2/FiO2 thresholds, respect linearly imputed PaO2/FiO2 thresholds. (13)

We therefore used this equation and included it in the statistical analysis plan to impute PaO2/FiO2 from non-invasive PaO2/SpO2, and programmatically categorize APLICOV-PC patients according to FDA guidance.

$$PO_2 = \left\{\frac{11{,}700}{\left(1/S - 1\right)} + \left[50^3 + \left(\frac{11{,}700}{1/S - 1}\right)^2\right]^{1/2}\right\}^{1/3} + \left\{\frac{11{,}700}{\left(1/S - 1\right)} - \left[50^3 + \left(\frac{11{,}700}{1/S - 1}\right)^2\right]^{1/2}\right\}^{1/3}$$

Fig 1. Ellis solution for the Severinghaus equation (S= SpO2 from pulse oximetry)

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"I have read this statistical analysis plan and confirm that to the best of my knowledge it accurately describes the analytical methods".

Reviewers:

NAME : Antonio Nieto
TITLE : Biostatistics Manager

Signature _____ date 22 MAR 2021

NAME: José A. Díaz Mazin
TITLE : Associate Director

Signature _____ date 22 MAR 2021

Approver:

NAME: Javier Gómez
TITLE : Sr. Manager. Biostatistics & Data Management

Signature _____ date 22 MAR 2021