Extension Study in a Cohort of Adult Patients With SARS-CoV-2 Infection Requiring Hospital Admission and Received Treatment With Plitidepsin in the APLICOV-PC Study

Study Protocol

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PROTOCOL CODE: E-APLICOV-PC/ AV-APL-A-003-21

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SPONSOR: Pharma Mar, SA

Previous versions of the protocol/amendments (number and date):

- Not applicable

Current version (number and date):

- Version 1.0 dated 06/Oct/2021

1. PROTOCOL SUMMARY

1.1.Sponsor identification

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1.2. Study Title

Extension study in a cohort of adult patients with SARS CoV2 infection requiring hospital admission and received treatment with plitidepsin in the APLICOV-PC study.

1.3. Protocol code

E-APLICOV-PC/ AV-APL-A-003-21

1.4. Drug Research Ethics Committee (CEIm)

Drug Research Ethics Committee of HM Hospitales

1.5. Company Responsible for Monitoring

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1.6. Investigational product

Plitidepsin

1.7. Clinical Trial Phase

APLICOV-PC proof-of-concept study follow-up.

1.8. Study objective

Evaluate the incidence of post-COVID morbidity and characterise the complications profile in patients who participated in the APLICOV-PC study.

1.9.Study design

Multi-site extension study of the APLICOV-PC clinical study follow-up.

The plitidepsin doses considered in this trial include the three doses specified in the APLICOV-PC study:

- 1.5 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days (total dose 4.5 mg).
- 2.0 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days (total dose 6.0 mg).
- 2.5 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days (total dose 7.5 mg).

1.10. Disease under study

COVID-19 infection or SARS CoV2 infection.

1.11. Endpoints

Incidence of post-COVID-19 complications.

1.12. Study population and total number of patients

The main objective of the study is to evaluate the incidence of post-COVID morbidity and characterize the complications profile in patients who participated in the APLICOV-PC study.

The maximum number of patients who can participate in the trial is limited to 42.

1.13. Inclusion and exclusion criteria

1.13.1. Inclusion criteria

Patient who participated in the APLICOV-PC study treated with plitidepsin and who gives their consent.

1.13.2. Exclusion criteria

There are no exclusion criteria for this study.

1.14. Study schedule

Inclusion start date: 10/2021

Inclusion end date: December 2021

The study will end with the last procedure performed on the last patient. It is estimated that all procedures will have ended in the month after the inclusion of the first patient in the study.

2. TABLE OF CONTENTS

3. ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AEMPS	Spanish Agency for Medicines and Health Products
AUC	Area Under the Curve
CEIm	Drug Research Ethics Committee
CK	Creatine-phosphokinase
CRF	Case Report Form
EC	European Community
ECG	Electrocardiogram
ECO	Ecocardiogram
eCRF	Electronic Case Report Form
eEF1A	Eukaryotic elongation factor
EU	European Union
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamate-pyruvate transaminase
HR	Heart rate
IC50	Inhibitory concentration 50
IC90	Inhibitory concentration 90
ICH	International Council for Harmonisation
ID	Identification number
LDH	Lactate dehydrogenase
mMRC	Modified Medical Research Council
MUGA	Multigated acquisition scan
PaFi Ratio	Ratio of partial pressure arterial oxygen and fraction of inspired oxygen.
PR	PR interval
Q1	First quartile
Q3	Third quartile
QT	QT interval

Abbreviation	Term
RR	Respiratory rate
SAE	Serious Adverse Event
SAFI	Ratio of percutaneous oxygen saturation to the fraction of inspired oxygen.
SaO2	Oxygen saturation
WHO	World Health Organisation
WMA	World Medical Association

4. STUDY CHARACTERISTICS

4.1. Study identification

Protocol code:

E-APLICOV-PC/ AV-APL-A-003-21

Title:

Extension study in a cohort of adult patients with SARS CoV2 infection requiring hospital admission and received treatment with plitidepsin in the APLICOP-PC study.

4.2. Study phase

APLICOV-PC proof-of-concept study follow-up.

4.3. Description of the investigational product

Plitidepsin.

4.4. Sponsor information

Name:

Pharma Mar, SA

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4.5. Drug Research Ethics Committee (CEIm)

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4.6. Company Responsible for Monitoring

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4.7. Expected duration of the study

Inclusion start date: 10/2021

Inclusion end date: December 2021

The study will end with the last procedure performed on the last patient. It is estimated that all procedures will have ended in the month after the inclusion of the first patient in the study.

5. JUSTIFICATION AND OBJECTIVES

5.1. Introduction

COVID-19

In December 2019, the World Health Organisation received information on a group of cases of pneumonia of unknown aetiology. The cause of this pneumonia was identified as a new virus in the Coronaviridae family (SARS CoV2) and the clinical picture associated with the virus has been named COVID-19.

In January 2020 the first case was reported in Spain and in mid-February the first patient died of it. The growth of confirmed cases has not stopped since then.

On 10 September 2021, the Coordination Centre for Health Alerts and Emergencies of the Ministry of Health reported that in Spain there have been 4,907,461 cases and 85,290 deaths [1].

COVID-19 is currently a public health emergency. The onset of a virus unknown until the end of 2019 has made it necessary to take measures taking into account the existing scientific knowledge with similar viruses and past situations.

APLICOV-PC study

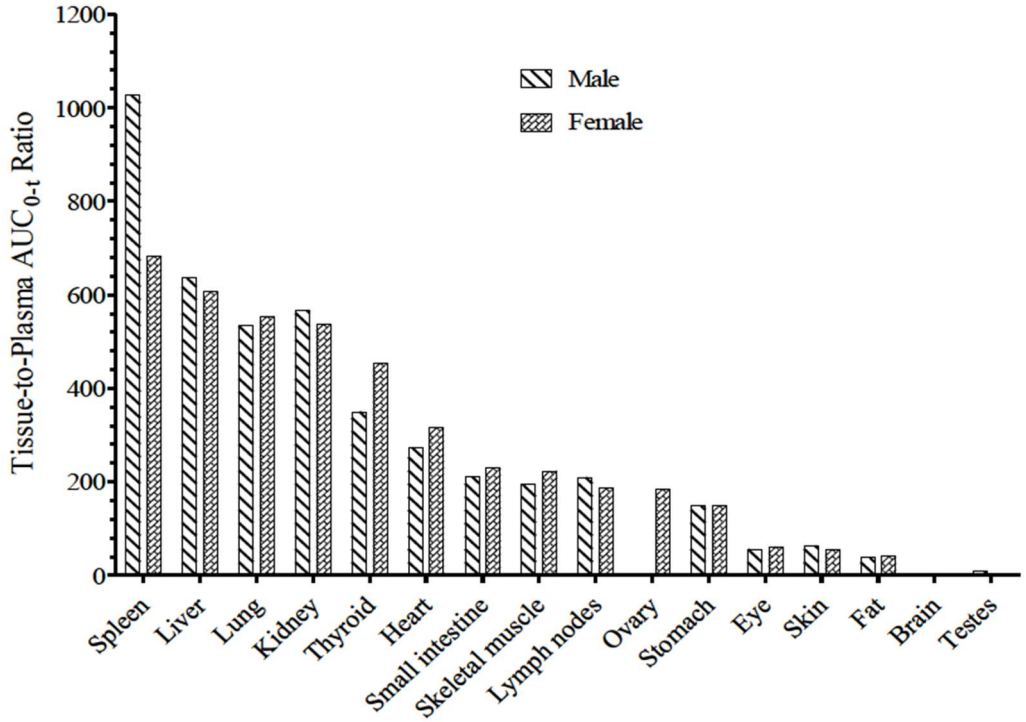
The APLICOV-PC proof-of-concept study of plitidepsin [2] has fulfilled the primary safety objective. The characterised range of doses, of 1.5, 2.0 and 2.5 mg/day x 3 consecutive days, confirms a positive therapeutic index in the study's target population (adult patients with COVID-19 infection requiring hospital admission), as well as a good tolerance to the treatment, and the absence of any differences in the level of safety between the 3 evaluated doses.

It is believed that the framework of pharmacological intervention proposed in the indicated group of patients could impact the natural course of the disease, based on:

- The dose range proposed according to the PK/PD model, anticipated that supra-pharmacological concentrations would be reached in distal anatomical compartments.

- The in-vivo biodistribution of plitidepsin confirms that key organs in SARS CoV2 are exposed to therapeutic concentrations (Fig. 1).

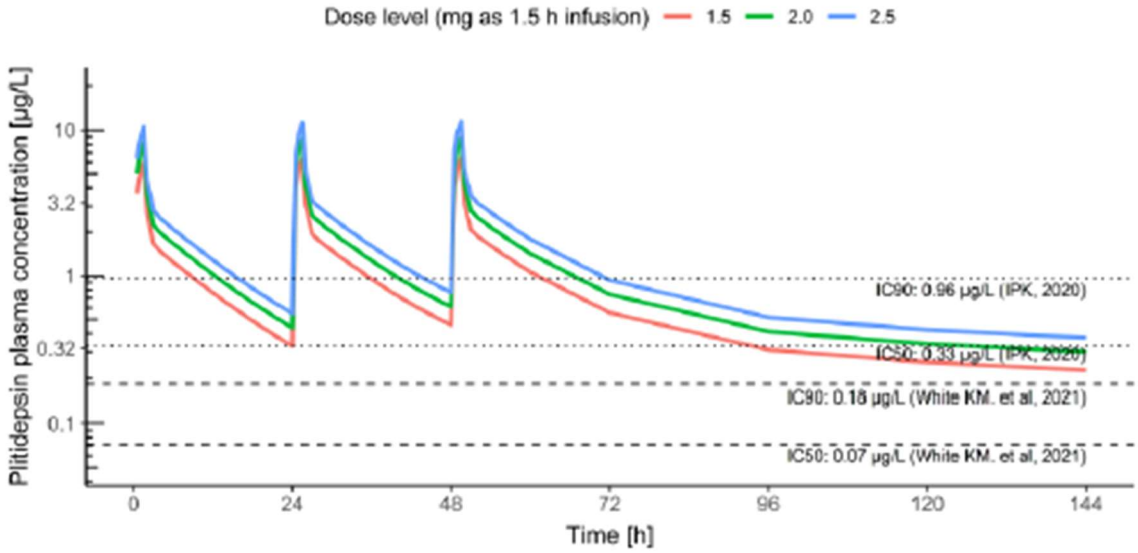
Figure 1. AUC_{0-t} of the Total Radioactivity in SD Rats (Both Sexes) after a Single Administration of an I.V. Bolus dose of $^{14}C_1$-Plitidepsin A 1.2 mg/m^2 (0.2 mg/Kg).



*For plasma AUC0-t, t=72 and 48 h in male and female rats, respectively.

- The terminal half-life exceeding 30 hours supports a pharmacologically valid model of exposure, administering the medication over 3 consecutive days. With all the three dosage levels used (1.5 mg, 2.0 mg and 2.5 mg), plasma concentrations above IC50 were obtained throughout the treatment period and remained above IC90 for most of the administration interval. The accumulation after three repeated administrations is minimal.

Figure 2. Total plasma concentration profiles vs. plitidepsin time predicted for the administration schedule and doses used in the APLICOV-PC study.



The horizontal lines represent the total plasma concentrations associated with lung concentrations equivalent to IC50, IC90 and 3xIC90 *in vitro*.

The APLICOV-PC proof-of-concept study has validated the proposed hypothesis in terms of impact on viral load (Fig. 3), full recovery / discharge from hospital rapidly induced (Fig. 4) and very relevant impact on lymphocyte reconstitution and other relevant inflammatory parameters (Fig. 5).

Figure 3. Effect of Plitidepsin and Remdesivir on viral load.

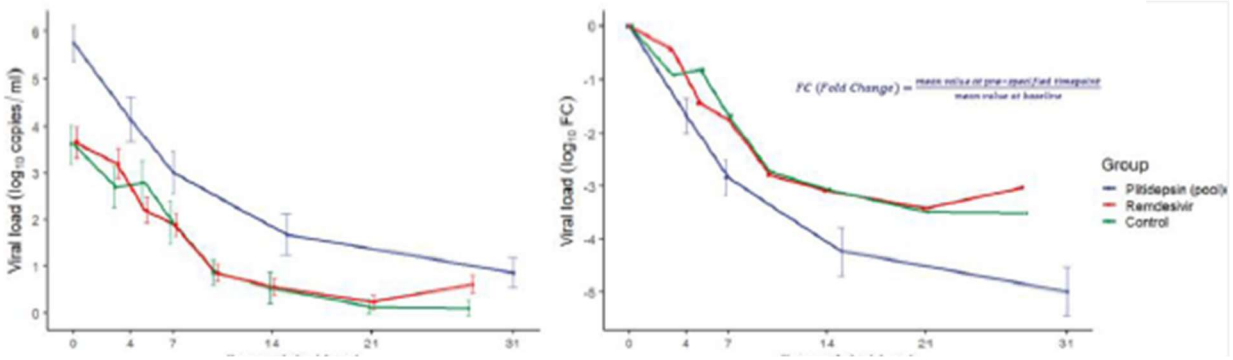


Figure 4. Time until discharge from hospital by dose and category (FDA)

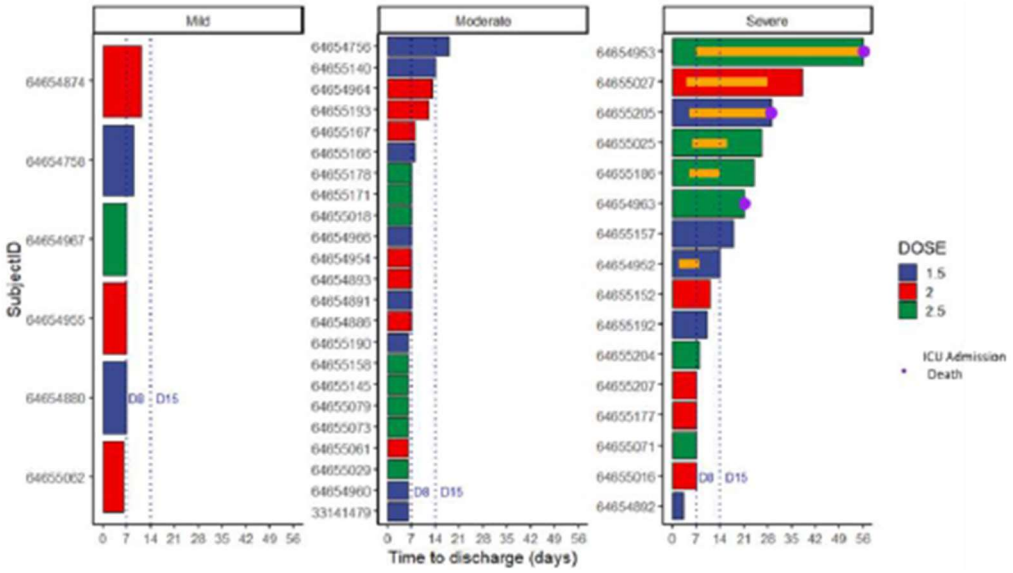
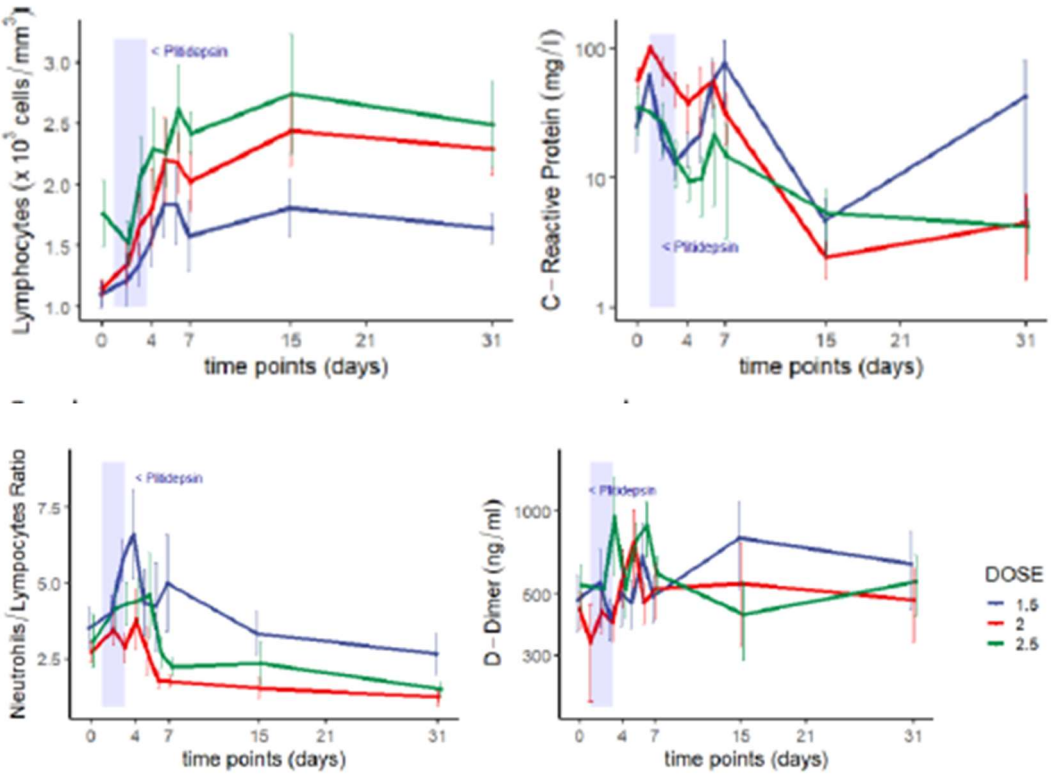


Figure 5. Inflammatory markers in APLICOV-PC patients: Effect of the Dose in Subjects with Moderate COVID-19 according to the FDA.



Therefore, these results generated in the APLICOV-PC proof of concept study are deemed to be compatible with consideration as a tangible post-COVID clinical benefit, in which reference is made to the prevention/minimisation of

complications related to the SARS CoV2 infection. Also, it should be highlighted that 87% of the patients had a moderate to severe illness when they entered the APLICOV-PC study and, on day 15, 82% of the patients had already been discharged.

The last patient was included in the APLICOV-PC study in November 2020. Therefore there is already an extensive margin of time for follow-up of almost 12 months, which justifies this study's approach.

The complications following SARS CoV2 infection represent a medical challenge. The evolutionary process following SARS CoV2 infection is critical in terms of the patient's quality of life, the emergence/persistence of morbidities, and social and pharmacoeconomic impact [3-5]. The potential impact of plitidepsin in controlling the sequelae arising from the SARS CoV2 infection is deemed sufficiently clinically relevant to justify the creation of this study.

Post-COVID 19 Syndrome

SARS CoV2 infection is a systematic process that goes beyond affecting the respiratory tract. COVID-19 complications and sequelae are very varied and increasingly frequent and better documented. Post-COVID sequelae occur after a severe SARS CoV2 infection in patients who required hospitalisation admission. They are generally a consequence of structural damage to different organs by the infection itself and/or associated complications. Various studies point to the sequelae of this infection not only restricting the respiratory apparatus: sequelae have also been recorded in the cardiovascular system, in the kidneys and in the central and peripheral nervous system [6-11]. Psychiatric and psychological sequelae have also been documented [12].

In patients who present a severe COVID-19 clinical picture, the main sequelae is the development of pulmonar fibrosis. According to a recent metaanalysis, approximately 30% of patients hospitalized with pneumonia due to SARS CoV2 have presented fibrotic changes that persist for the first 12 months after discharge from the hospital [13].

It has been documented that patients with severe forms of COVID-19 presented significant heart injuries, including myocarditis related to infection, with a reduced systolic function and arrhythmias. Myocardial injury has been reported, which may be due to direct damage to the cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, and hypoxia [14]. Due to significant myocardial injuries in patients with severe clinical symptoms due to COVID-19, the morbidity and lethality of the illness could be high [15-17].

In severe cases of COVID-19, the systemic hyper-inflammatory response could cause long-term cognitive damage, such as, for example, memory loss, attention deficit, slower processing speed associated with cognitive functioning, along with diffuse neuronal loss [18]. Various types of neuropsychiatric clinical signs have also been observed, such as encephalopathy, mood swings, psychosis, neuromuscular dysfunction or demyelinating processes. These may accompany an acute viral infection, or may emerge weeks, months, or even later, post-

infection, in recovered patients [19-21]. According to an electronic follow-up record of 236,379 patients during the first six months following COVID-19 diagnosis, neuropsychiatric complications emerge in 34% of cases, not including cephalea. The most common complications include mood and anxiety disorders and psychoses (24%), neuropathies (2,1%), ischaemic heart disease (2.8%) and dementia (0.67%) [22]. On the other hand, the most frequent neurological symptoms are cephalea and cognitive changes, described in up to 68% and 81% of patients, respectively, with some sort of neurological symptom after week 12 following acute infection [23]. Cognitive changes that are usually reported are lack of concentration, attention, or difficulty planning tasks.

The rapid drop in viral load of patients with COVID-19 infection may reduce the frequency of complications caused by the infection in the following months [24].

The WHO European Observatory on Health Systems and Policies estimates that 10% of infected patients remain symptomatic for at least 12 weeks after infection, resulting in long-term sick leave, leaving sequelae that in 0.8% even last more than a year [25]. A study in Spain, based on Social Security data, shows that COVID caused 1.2 million registered sick leaves by March 2021, and its authors indicate that nearly 100,000 people needed 12 weeks or more to recover from post-COVID sequelae. The casualties were justified by almost 50 different symptoms ranging from fever, shortness of breath, fatigue, anxiety, dizziness or memory loss.

On the other hand, data has been published from the COVERSCAN study conducted in the United Kingdom [25], which carried out serial Magnetic Resonance Imaging (MRI) scanning in a sample of 201 generally-healthy, middle-aged individuals, with COVID-19. The investigators found evidence of mild organ impairment of the heart (32%), lungs (33%), kidneys (12%), liver (10%), pancreas (17%), and spleen (6%) and reported that nearly 70% of the individuals suffered impairment in one or more organs 4 months after the initial symptoms of SARS-CoV2 infection, which was higher than age-matched healthy controls.

5.2. Justification of the study

As previously indicated, the APLICOV-PC proof of concept study demonstrated the antiviral activity of plitidepsin in terms of reducing viral load, inducing recovery, and impact on lymphocyte reconstitution and other inflammatory parameters.

A percentage of patients, which varies between 10 and 25%, continue to show symptoms at 3 months after contracting the SARS CoV2 infection: For some of them this significantly restricts their life, requiring them to take long-term sickness leave from work, and leaving them with sequelae that may continue for more than one year.

With this study, we intend to evaluate whether the treatment with plitidepsin, by attaining a reduction in the viral load and a faster recovery of the patient, could have a relevant impact on the emergence of sequelae resulting from the SARS CoV2 infection.

5.3. Study objectives

Evaluate the incidence of post-COVID morbidity and characterise the complications profile in patients who participated in the APLICOV-PC study.

6. STUDY DESIGN

6.1. Design

Multi-site extension study of the APLICOV-PC clinical study follow-up.

The plitidepsin doses considered in this trial include the three doses specified in the APLICOV-PC study:

- 1.5 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days (total dose 4.5 mg).
- 2.0 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days (total dose 6.0 mg).
- 2.5 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days (total dose 7.5 mg).

6.2. Primary endpoint

Incidence of complications related to COVID-19 infection.

Evaluation of the principal variable:

The following information will be gathered in this study:

- Readmissions to hospitals and causes, from the last visit of the APLICOV-PC study to the end of the extension study.
- Need for oxygen therapy and duration of the same, from last visit of APLICOV-PC study until the end of the extension study.
- Presence of complications (see annex 5) since last visit of APLICOV-PC study until the end of this extension study by the patient.

Also, once the informed consent has been signed, the following tests will be carried out in the following 7 days:

- Barthel Index [26], to assess the patient's degree of autonomy when performing activities of daily living.
- Evaluation of the dyspnea, according to the mMRC scale [27].
- Evaluation of functional capacity (6 minute walk test) [28].
- Physical examination, including weight, height, BSA, pulse oximetry, PAFI (estimated annex 8).

- Full analysis, including inflammation markers.
- Chest X-ray, in patients diagnosed with pneumonia upon admission to hospital, which led to their participation in the APLICOV-PC study.
- Evaluation of pulmonary function, including dyspnea evaluation (mMRC and 6 minute walk test) (annexes 7 and 9) SaO2, PAFI (direct or estimated) (annex 8), spirometry (forced vital capacity, FEV1 and FEV1/CVF) and the diffusion test.
- Electrocardiogram.
- Heart Ultrasound/MUGA, in patients that suffered a relevant cardiac event while participating in the APLICOV-PC study or in those patients for which it was clinically indicated during follow-up.
- Thus, an evaluation was made of both the ultrasound images and the results of the complementary (analytical or functional) tests necessary for interpreting the long-term evolution of the disease, from the start of the patient's participation in APLICOV-PC to the end of this study.

6.3. Secondary outcomes

Not applicable.

7. SCREENING OF PATIENTS

All patients who participated in and received plitidepsin in the APLICOV-PC study are eligible candidates for participating in this extension study. The investigative team will contact the patient to agree a date for the medical visit. The patient will be invited to participate in the study, and be handed the Patient Information Leaflet for the same, along with all additional information related to the study that is necessary for obtaining their informed consent.

7.1. Inclusion criteria

Patient who participated in the APLICOV-PC study, who has been treated with plitidepsin and gives their consent.

7.2. Exclusion criteria

There are no exclusion criteria for this study.

7.3. Randomisation procedures

Not applicable.

7.4. Masking procedures

Not applicable.

8. WITHDRAWAL AND DISCONTINUATION CRITERIA

8.1. Reason for withdrawal

Patients will be excluded or withdrawn from the study for any of the following reasons:

- Withdrawal of consent by the patient.

All cases of a patient's withdrawal from the study must be documented in the Case Report Form.

8.2. Replacement of subjects and reserve subjects

Not applicable. Given the characteristics of the study, those patients who do not agree to participate in the study, or who withdraw their consent, cannot be replaced.

9. INVESTIGATIONAL PRODUCT

9.1. Description of the investigational product

Plitidepsin is licensed in Australia for the treatment of multiple myeloma.

Plitidepsin is currently being investigated in a study to assess the efficacy and safety of the different doses vs a control arm in patients with moderate COVID-19 infection (NEPTUNO). It is a randomized open-label phase III study in adult patients who require hospitalisation and oxygen supplement to treat a moderate COVID-19 infection. The study is designed to evaluate the safety and efficacy of plitidepsin at a low dose (1.5 mg x 3 days) and at a high dose (2.5 mg x 3 days), and it will be compared with the control arm.

Also, plitidepsin was previously studied in the APLICOV-PC COVID-19 study, a proof of concept clinical trial to evaluate the safety of three doses of plitidepsin (1.5 mg, 2.0 mg and 2.5 mg administered over 3 consecutive days), in adult patients hospitalized for COVID-19 [2]. The aim of this study was to determine the safety and toxicological profile, as well as the efficacy, of each dosage level. The results of this clinical trial indicated a positive benefit-risk ratio for the treatment of COVID-19 infection, given the low incidence of adverse events related to the drug of grade ≥ 3, and the high proportion of discharges from

hospital on days 8 and 15, together with a significant drop in viral load, with no significant differences observed among the three dosage groups.

9.1.1. Description

Plitidepsin is a powder for concentrate for solution for infusion at a concentration of 2 mg/vial.

9.1.2. Packaging

Plitidepsin 2 mg is presented in a Type I clear glass vial with a bromobutyl rubber stopper covered with an aluminium seal. Each vial contains 2 mg of plitidepsin.

The solvent for the reconstitution of macrogolglycerol ricinoleate (polyoxyl 35 castor oil)/absolute ethanol/water for injection, 15%/15%/70% (v/v/v) is supplied in a Type I colourless glass vial. The ampoules have a volume of 4 ml.

9.1.3. Shipping and storage

Plitidepsin should be stored between 2ºC and 8ºC and the vials should be kept in the outer carton to protect them from light.

The drug in these conditions is stable for 60 months.

9.2. Dosage and administration

The patients included in the extension study received no treatment whatsoever in relation to the study. To participate in the study, the patients must have previously participated in the APLICOV-PC proof of concept study and may have received:

- 1.5 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days.
- 2.0 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days.
- 2.5 mg of plitidepsin administered as a 1.5-hour infusion, once a day for 3 consecutive days.

9.3. Duration of treatment

Not applicable.

9.4. Criteria for dosage modification

Not applicable.

9.5. Treatment accounting and compliance

Not applicable.

9.6. Prohibited drugs

Not applicable. Patients who participate in this extension study may be receiving the medicines that their doctors deem necessary.

9.7. Drug interactions

Not applicable, as no medication is administered in this clinical trial.

10. EVALUATION CALENDAR

	Baseline	Up to day +7
Informed consent[1]	X	
Selection criteria[2]	X	
PCR COVID-19[3]		X
Medical history review[4]		X
Vital signs[5]		X
Physical examination		X
Symptoms/signs/complications of the disease [6] (annex 5)		X
Neurological examination		X
Pulmonary function[7]		X
Barthel scale		X
Electrocardiogram[8]		X
Haemogram and differential count[9]		X
Biochemistry[10]		X
Coagulation[11]		X
C-reactive protein		X
Chest x-ray[12]		X
SARS CoV2 IgG Serology		X
Ultrasound / MUGA[13]		X
Other pharmacological treatments [14]	X	X
Adverse events[15]		X
Hospital readmissions[16]	X	
Need for oxygen therapy[16]	X	
X-rays / complementary tests[17]	X	

1 The patient will sign the informed consent before undergoing any specific study procedure that is not part of normal clinical practice.

2 The patient must meet all the inclusion criteria in order to be included in the study.

3 It will be confirmed via a PCR test that the patient has no COVID infection at the moment of being recruited to the study.

4 The code assigned to the patient for participation in the (APLICOV-PC) reference study will be recorded. It will be confirmed if the patient has presented new COVID-19 episodes since the study ended, and if they have been vaccinated / the type of vaccine / received doses. Details of hospital readmissions and causes and the need for oxygen therapy were collected, from the last visit of the APLICOV-PC study to the signing of the informed consent form, and subsequently to the end of the study.

5 Vital signs: temperature, arterial tension, heart rate, respiratory rate.

6 Presence of complications (see annex 5) since the last visit of the APLICOV-PC study until the end of this extension study.

7 Evaluation of pulmonary function, including dyspnea evaluation (mMRC and 6 minute walk test) (annexes 7 and 9) SaO2, PAFI (direct or estimated) (annex 8), spirometry (forced vital capacity and FEV1) and the diffusion test.

8 The electrocardiogram: overall evaluation and measurement of PR, QT and RR intervals. Save the ECG in the patient's history.

9 Complete blood count, including inflammation markers.

10 It will include creatinine, ions, calcium, albumin, transaminases, bilirubin, alkaline phosphatase, LDH, CK, ferritin and troponin.

11 It will include D-dimer.

12 A chest X-ray will be taken for patients diagnosed with pneumonia upon admission to hospital, which led to their participation in the APLICOV-PC study.

13 A heart ultrasound / MUGA will be performed on patients who suffered a relevant cardiac event during their participation in the APLICOV-PC study.

14 All pharmacological treatments received by the patient since the last visit of the APLICOV-PC study to the signing of the informed consent form, will be collected.

15 Serious and non-serious adverse events related to the study procedures, from the signing of the informed consent until the end of the patient's participation in the study, will be collected.

16 If the patient so requested, their hospital readmissions/oxygen therapy, since the last visit of the APLICOV-PC study to the signing of the informed consent for the extension study, will be collected.

17 Collection of ultrasound images or the results of complementary (analytical or functional) tests necessary for interpreting post COVID-19 evolution.

11. ADVERSE EVENTS

No adverse effects were expected in this study, as no adverse events suspected of being related to plitidepsin in the treated patients have been reported since the APLICOV-PC study ended. However, if an adverse effect is observed that may be related to the study procedures, pharmacovigilance will be notified according to the current regulations.

12. STATISTICAL CONSIDERATIONS

12.1. General considerations

This section describes the main analyses that will be carried out. The statistical analysis plan to be approved by the sponsor will include additional information on analyses, management of unavailable data and analytical methods. All data will be analysed with the SAS statistical analysis system, version 9.4. All analyses will be carried out mainly by descriptive statistical methods. Continuous endpoints will be described using maximum, minimum, Q1 and Q3, mean, median and standard deviation. Categorical endpoints will be described with frequencies and percentages as well as the exact 95% confidence interval of the relevant study variables. All results will be presented separately by treatment arm and severity of the information upon entry into the APLICOV-PC study.

The final statistical study that will be the basis of the study's final report, will cover the total population of patients once the extension study has ended.

12.2. Sample size

The main objective of the study is to evaluate the incidence of post-COVID morbidity and characterize its profile in patients who participated in the APLICOV-PC study. Given that a total of 45 patients received plitidepsin in said study, of which 3 died as a consequence of the progression of the disease, the maximum number of patients who could participate in the study is limited to 42.

Assuming an average incidence of post-COVID complications of 15%, this study would have a power of 80% for detecting a reduction of 10%: if 3 or less patients presented post-COVID complications, the study would reject the null hypothesis (incidence of post-COVID complications: 15%) and would accept the alternative (5%), with an alpha error of 0.05 (unilateral).

12.3. Analysis populations

All patients who sign an informed consent form and agree to undergo the battery of clinical examinations, imaging and laboratory tests specified in section 10 of the protocol, will be analysed in order to fulfil the objectives of the study.

12.4. Analysis of the primary endpoint

The main objective of the study is to evaluate the incidence of post-COVID morbidity and characterize the complications profile in the cohort of patients who participated in the APLICOV-PC study.

The number and percentage of patients who develop complications related to persistent illness, as judged by a physician, during the period between the end of the APLICOV-PC proof of concept study and the end of this extension study by the patient, as well as the percentage of patients who present complications.

A description of the following endpoints will also be presented:

- Number and percentage of patients who required readmission to hospital and causes, since last visit of APLICOV-PC study until the end of this extension study.
- Need for oxygen therapy and duration of the same, since last visit of APLICOV-PC study until the end of this extension study.
- The maximum, minimum, Q1 and Q3, mean, median and standard deviation of the duration of the oxygen therapy will be provided.
- Number and percentage of patients who presented complications (see annex 5).
- Barthel Index [26]. A description will be provided with the frequency and percentage of each dependency category according to the score obtained:

  0-20: Total dependency
  21-60: Severe dependency
  61-90: Moderate dependency
  91-99: Slight dependency
  100: Independence
- The maximum, minimum, Q1 and Q3, mean, median and standard deviation of the parameters related to pulmonary function will be provided: SaO2, PAFI, CVF, FEV1, FEV1/CVF and diffusion test.
- The maximum, minimum, Q1 and Q3, mean, median and standard deviation of the results of the 6 minute walk test will be provided.
- A description will be provided with the frequency and percentage of each category of the mMRC scale.
- Number and percentage of patients with abnormalities in the chest X-ray, in patients who present pneumonia upon entry into the APLICOV-PC study, and description of the abnormalities.
- Number and percentage of patients who presented abnormalities ≥G2 in the analytical parameters.
- Number and percentage of patients who presented abnormalities in the ECG, and description of the abnormalities.
- Number and percentage of patients who presented abnormalities in the heart Ultrasound/MUGA in patients who suffered a relevant cardiac event during their participation in the APLICOV-PC study, and description of the abnormalities.

The endpoints listed were correlated with the patients' basal characteristics, the degree of severity of the illness, comorbidities, the plitidepsin dosage, the viral load and the clinical evolution documented in the APLICOV-PC study.

13. DATA MANAGEMENT AND QUALITY ASSURANCE

13.1. Clinical trial monitoring and audits

The sites participating in the study will be supervised by monitors appointed by the sponsor, with specific training for this clinical trial, making periodic visits to the site before, during and at the end of the trial. These monitoring visits will be carried out in accordance with the International Council for Harmonisation (ICH) E6 (R2) guidelines. Visits can be supplemented by telephone contact or written communication. In this study, remote verification of source data may be performed in agreement with the participating centres.

Priority will be given to centralised monitoring and/or remote monitoring of the participating sites, avoiding overloading the site staff with tasks or reviewing source data and postponing, as far as possible, the verification of source data until it is possible to access the medical history directly. The sponsor will agree the conditions for such monitoring with the participating sites and teams.

Procedures will be established to ensure the quality of any aspect related to the trial.

13.2. Audits

During the clinical trial, the Quality Department of Pharma Mar S.A. or external auditors contracted by the sponsor may make audit visits to the site, either in person or remotely.

13.3. Inspections

Participation in this clinical trial implies acceptance of possible inspection by national or foreign regulatory authorities.

13.4. Reporting of serious breaches

Any serious breaches of the authorised protocol or of Royal Decree 1090/2015 that occur in Spain must be reported by the sponsor without undue delay and no later than seven calendar days from detection of the breach to the Spanish Agency for Medicines and Medical Products (AEMPS) and the CEIm.

For this purpose, a serious breach will be defined as any non-compliance that may significantly affect the safety and rights of the study subjects or the reliability and integrity of the data generated in the clinical trial.

Only serious breaches will be reported to the AEMPS and the CEIm, and breaches that do not constitute a serious breach will not have to be reported.

Each investigator has to document and explain in the clinical history of the subjects any breach to the approved protocol and/or Royal Decree 1090/2015. Investigators can implement a protocol breach to eliminate an immediate safety risk to the subject without prior CEIm approval, but such a breach must be reported to the study monitor within one business day. These incidents will be evaluated and, if appropriate, an amendment to the protocol will be prepared.

The monitor will document breaches during monitoring visits. The monitor will notify the investigator of the breach during the visit and the “Breach Form” document will be completed and signed by the investigator and monitor.

13.5. Data management

APICES will be responsible for processing and quality control of the data. Data management will be performed according to the Data Management Plan, standard operating procedures and the current regulations.

Data management based on Good Clinical Practice (GCP) standards refers to the activities defined to achieve safe routines for the efficient input of information in the study database, avoiding errors. Routines include procedures for CRF handling, application design and management, data entry and verification, data validation, database quality control and documentation of activities performed, including information on discrepancies found during the process. The database, data input screens and programming will be designed by APICES in accordance with the clinical trial protocol.

13.6. Electronic Case Report Forms (eCRF)

The collection of study data will consist of the electronic recording of all the information required by the eCRF. APICES will provide the eCRF.

All investigators agree to keep eCRFs filled in with truthful and accurate information as well as source documents that are part of medical records.

All the requested information must be completed in each patient's eCRF. If a patient is included in the study but withdraws their consent, only the minimal data will be collected in the CRDe, such as demographic data and the date of informed consent, as well as the reason for the withdrawal, if the patient does not mind providing it. In general, no queries will be issued for the data of these patients indicated in the eCRF as “Not done” or “Not available”.

For the patients included in the study, the information from the source documents will be included in each patient's eCRF by the staff of the investigation team of the site for this study and this information will be supervised by an APICES monitor. If the information requested on any variables is not available or does not apply, the reason must be included. Data should not be missing unless otherwise stated. Modifications to the eCRF must be made following the procedure described in the eCRF user guide and will be recorded in the eCRF.

Each completed eCRF must be reviewed, signed and dated by the Principal Investigator of the study without delay. The completed eCRF will be reviewed by the study monitor as soon as possible after completion. The site will be provided with an electronic copy of the final, approved and signed eCRF, which must be stored in the corresponding file.

13.7. Web-based electronic CRF

The data collected in this clinical trial will be entered into an application designed to collect study data. Access to the eCRF is password protected and includes internal quality controls, such as automatic data entry range controls, to identify inconsistent, incomplete or inaccurate data. The clinical data will be entered in the application based on the source documents. The profiles and data entry permits for the eCRF at each participating site will be established in advance. Only study staff from each site designated by the principal investigator will be authorised to enter the data in the eCRF. The principal investigator and the research team will receive the necessary training to complete the eCRF and will be informed, before the start of the study and before any study data are entered in the eCRF, of the security measures that they must take into account.

13.8. Data recording in the electronic CRF

All data must be entered in Spanish. The eCRFs must always reflect the latest observations of the patients participating in the study. Therefore, the eCRFs should be filled in as soon as possible during or after the patient's visit. The principal investigator of each participating site must check that all the data entered in the eCRFs are accurate and correct.

If some evaluations are not carried out, or if certain information is not available, not applicable or unknown, the investigator or any other authorised person must state it in the eCRF. The investigator will approve the data by means of an electronic signature, and this approval will serve to confirm the accuracy of the recorded data.

13.9. Query management

The monitor will review the eCRFs and evaluate their completion and consistency. Each eCRF will be compared against the respective source documents to ensure that there are no discrepancies in critical data. The investigator or other authorised personnel will carry out the data entry, corrections and modifications. The monitor cannot fill in data in eCRFs.

Once the clinical data of the eCRF have been recorded in the application, the corrections made to each of the variables will be recorded in the audit trail (e.g. the reason for any change, the name of the person who made the change, the time and date). If additional corrections to the data are required, the monitor in charge at the site or the data manager will include a query in the eCRF. The authorised site personnel will answer the queries

generated in the application. This entire process will be recorded in the audit trail along with the name of the person who made the change, the time and the date.

13.10. Source documents

The eCRF is essentially considered a data entry form and should not replace the original medical records (or source document) unless otherwise specified in the study protocol. Source documents are all documents used by the investigator or the hospital that relate to the patient's medical history, which verify the patient's existence, the inclusion criteria, and all the records that justify the patient's participation in the study. These include the inclusion of the patient, analyses, laboratory tests and images, the patient's file, questionnaires about symptoms, etc.

Each investigator is responsible for maintaining source documents. These will be available for inspection by the study monitor at each monitoring visit, which may be carried out in person or remotely. All additional documentation completed in the eCRF, such as laboratory data, must be clearly identified with the study, visit and patient number. Any personal information (e.g. subject's name, initials) must be removed or redacted to preserve patient confidentiality.

13.11. User identifier

In each record included in the eCRF, the user's identification will be automatically added through their unique ID. The data for each of the patients included in the study will be electronically signed by the investigator to document their review and confirmation that the data are accurate. This will be done using the Investigator's ID and password; the date and time of signing will be automatically added at the time of the electronic signature. Should it be necessary to modify data in an eCRF, the correction must be made according to the procedures of the software used.

13.12. Change control

To comply with regulatory requirements, eCRF data will be electronically filed in the file of each participating site. All changes are recorded in a protected audit trail, and it will be necessary to enter the reason for the change. Once all data have been entered, verified and validated, the database will be locked to prevent further changes to the study data.

13.13. Documentation storage

Essential documents and eCRF data should be kept for 25 years after the end of the trial, or for a longer period if other requirements apply, such as if the study is presented as a basis for drug registration in which Annex I of Royal Decree 1345/2007, of October 11, must be complied with.

The clinical history of the test subject must be kept in accordance with the provisions of Law 41/2002, of November 14, and according to the maximum period allowed by the hospital, institution or private practice.

14. ADMINISTRATIVE CONSIDERATIONS

The following administrative aspects are intended to guide the investigators participating in the study, but may be subject to changes based on the sponsor's procedures, legislation, or working documents or guidelines.

14.1. Legal Considerations

This clinical trial will be carried out in accordance with the ethical principles in the Declaration of Helsinki developed by the World Medical Association (WMA) and following the standards of good clinical practice and applicable legislation.

The staff involved in conducting this trial will be trained and have sufficient experience to perform the necessary tasks.

The study will be carried out in accordance with the protocol. The protocol, any amendment and the informed consent form will be approved by a CEIm before the start of the study, in accordance with current legislation.

The decision of the CEIm on the execution of the study will be stated in writing. The investigator and/or sponsor are responsible for keeping the CEIm informed of any relevant information about the study drug. All protocol amendments will be agreed upon by the sponsor and the investigator.

Administrative changes to the protocol are considered minor corrections and/or clarifications that have no impact on the way the study will be conducted.

14.2. Review by the Drug Research Ethics Committee

The ICH guidelines require the approval of the health authorities and a favourable opinion from an accredited Clinical Research Ethics Committee (in Spain CEIm) before patients can be included in clinical trials. Before the start of the study, the protocol, the informed consent form, the materials that will be used for patient recruitment (if applicable) and any other written information regarding the trial that is provided to the patient will be approved by the CEIm. The clinical trial can only be started when both the Health Authorities and the CEIm have considered that the expected benefits for the study patients and society justify the risks; in addition, this criterion must be continuously reviewed to continue with the trial with guarantees.

APICES will obtain the favourable opinion of the CEIm on behalf of the sponsor and the investigators. All regulatory approvals will be signed by the President of the CEIm, or the person appointed by them, and must identify the name and address of the CEIm, the trial protocol using the protocol title and/or code, and the date of approval or date on which the favourable opinion is granted. Documentation related to authorisation by the CEIm and the health authorities and CEIm compliance with ICH E6 (R2) guidelines will be kept at the site and will be available for review.

14.3. Protocol modifications

Any change to the approved protocol will require an amendment to the protocol. The investigator should not make any changes to the study without the favourable opinion of the CEIm and the authorisation of the health authorities (if applicable), except when necessary to eliminate an imminent and obvious risk for the patients or in the case of administrative changes. Modifications to the protocol to eliminate an imminent and obvious risk can be implemented immediately, but must subsequently be documented in an amendment, notified to the CEIm and the relevant health authorities within the required period.

Any major modifications to the protocol must be sent to the CEIm and the health authorities for approval before the changes proposed in the amendment can be applied. Depending on the magnitude of the change, recruitment could be temporarily suspended.

The sponsor does not have to notify minor modifications to the health authorities or the CEIm. However, a record will be kept of minor modifications, filed with the study documentation and notified when sending another notification or when a major modification is submitted. Documentation related to minor modifications will be available for inspection in the study file at the site or at the sponsor's facilities.

14.4. Informed consent

Before the patient is included in the study or before any specific procedure is carried out, informed consent must be obtained in writing from the patient or their legal representative, in accordance with ICH E6 guidelines.

For obtaining and documenting informed consent, the investigator must comply with applicable legislation, and must adhere to the standards of Good Clinical Practices as well as the ethical principles of the Declaration of Helsinki. The patient information leaflet and the informed consent form and any revisions thereof must be approved by the CEIm before being given to patients who are deemed eligible to participate in the study or to their legal representatives.

The sponsor will provide the investigation team of each participating centre with the patient information leaflet and the informed consent form approved by the CEIm.

Before performing any study procedure on the patient, it is the responsibility of the principal investigator (or person appointed by them) to obtain consent, freely given in writing, from the patient or their legal representative after adequately explaining the objectives, methods, expected benefits and potential risks of the study and before any protocol-specific screening procedure is performed or study drug is administered. Patients or their legal representatives should have the opportunity to ask questions and receive the requested information, and they will have sufficient time to decide whether or not they want to participate in the study. Once the investigator makes sure that the patient understands the implications of participating in the study, they will be asked to sign the informed consent in order to obtain their consent to participate in the study.

The informed consent form must be personally signed and dated by the patient or their legal representative and by the study doctor who carried out the informed consent process (Principal Investigator or appointed person).

The acquisition of written informed consent must also be documented in the patient's medical history.

The investigator must provide a copy of the signed informed consent form to the patient or their legal representative. Another original copy of the document will be filed in the investigator's study file at the site.

If the informed consent form is reviewed and modified during the study, active participating subjects must sign the document reviewed and approved by the CEIm.

The patient participating in the clinical trial, or their legal representative, can withdraw consent at any time, without giving any explanation and without this entailing any harm to the patient.

14.5. Confidentiality

The collection and processing of personal data of the patients included in this clinical trial will be limited to the data that are necessary to investigate the efficacy, safety, quality and usefulness of the study medication used in this trial.

It is the investigator's responsibility to keep sufficient information to allow patient identification.

The trial monitor, sponsor auditors, CEIm and Competent Authorities should have direct access to all trial-related information and agree to keep the identity of study patients confidential.

The data must be collected and processed with the appropriate precautions to guarantee confidentiality and compliance with the current legislation regarding data privacy.

Explicit consent of the patients or their representatives for the treatment of personal data will be obtained before data collection, if necessary, and this consent will include the transfer of the data to other companies and countries.

Pharma Mar SA will comply with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and with Organic Law 03/2018 on protection of personal data and guarantee of digital rights.

14.6. Insurance policy

The sponsor has contracted an insurance policy to cover the responsibilities of the investigators and the other parties participating in the study in accordance with the applicable regulatory requirements.

14.7. Publications

Before the investigators of this study send a manuscript or abstract for publication or publicly disclose information related to the study drug or products, they will provide this publication to Pharma Mar SA at least 60 days beforehand for review and approval, to guarantee that confidential data and data ownership are protected.

If Pharma Mar SA determines that any patentable aspect is disclosed in the proposed publication or communication, it will withhold the publication or communication for a period of time that it deems appropriate. If the study is part of a multi-site study, the first publication of the study will be carried out with the overall results of the study, taking into account the investigators and institutions of all participating centres that have contributed data, analysis and comments. However, if such publication of the global results is not presented within 12 months after the end of the study in all the sites, the study could be published individually according to the procedure established above.

The order of the co-authors will reflect the relative contribution of each of them in the development of the study and in the analysis. In general, the first author will be the investigator who has recruited the largest number of patients with information that is ultimately available for data analysis. Pharma Mar SA staff who have fully participated in the study should be considered for co-authorship in the publication.

15. ACCEPTANCE OF THE PROTOCOL BY THE SPONSOR

Clinical trial title: Extension study in a cohort of adult patients with SARS CoV2 infection requiring hospital admission and received treatment with plitidepsin in the APLICOP-PC study

Protocol Code: E-APLICOV-PC/ AV-APL-A-003-21

Version (number and date): 1.0 of 6 October 2021

Position (pre-printed name)	Signature	Signature Date (DD-Mmm-YYYY)
Position (pre-printed name)	Signature	Signature Date (DD-Mmm-YYYY)
Position (pre-printed name)	Signature	Signature Date (DD-Mmm-YYYY)

16. ACCEPTANCE OF THE PROTOCOL BY THE PRINCIPAL INVESTIGATOR

Clinical trial title: Extension study in a cohort of adult patients with SARS CoV2 infection requiring hospital admission and received treatment with plitidepsin in the APLICOP-PC study

Protocol Code: E-APLICOV-PC/ AV-APL-A-003-21

Version (number and date): 1.0 of 6 October 2021

I have read and carefully reviewed the study protocol. Having read and understood the requirements and conditions of the study protocol, I agree to carry out the clinical study according to the international principles of Good Clinical Practice and the requirements of the regulatory authorities for the verification of the original documents and the audit/inspection of the study. I agree to use the study material, including the medication, only as specified in the protocol.

I understand that the changes made to the protocol must be made in the form of an amendment with the sponsor's prior written approval. I understand that any breach of the protocol may lead to early termination of the study.

Signature of the Principal Investigator	Signature Date (DD-Mmm-YYYY)
Investigator's name (uppercase)	

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Annex 1. Declaration of Helsinki

WMA Declaration of Helsinki - Ethical principles for medical research involving human subjects

Adopted by the
18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Introduction

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician’s knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimises possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the investigator.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the investigator, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The investigator must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the investigators must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the investigator, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
    All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons

capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.
30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, investigators and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Annex 2. List of Sites / Principal Investigators

Attached in a separate document.

Annex 3. Sample Patient Information Sheet and Informed Consent Form

Attached in a separate document.

Annex 4. NCI-CTCAE criteria

The common terminology criteria for the classification of adverse events version 5.0 (NCI-CTCAE v. 5.0) can be consulted at the following Internet address:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Annex 5. Post-COVID complications

	List of post-COVID complications		
COMPLICATIONS	**HAVE HAD**	**Duration**	**Worst grade**
Fatigue/asthenia	YES/NO	Start/end date	
General malaise	YES/NO	Start/end date	
Headaches	YES/NO	Start/end date	
Low mood	YES/NO	Start/end date	
Muscle aches and pains	YES/NO	Start/end date	
Joint pains	YES/NO	Start/end date	
Attention deficit	YES/NO	Start/end date	
Chest pressure	YES/NO	Start/end date	
Anxiety	YES/NO	Start/end date	
Febricula	YES/NO	Start/end date	
Cough	YES/NO	Start/end date	
Memory lapses	YES/NO	Start/end date	
Diarrhoea	YES/NO	Start/end date	
Palpitations	YES/NO	Start/end date	
Dizziness	YES/NO	Start/end date	
Tingling in extremity	YES/NO	Start/end date	
Others (specify)	YES/NO	Start/end date	

List based on the survey carried out by the Spanish Society of General Practitioners and Family Doctors.

Annex 6. Barthel Index

ÍNDICE DE BARTHEL

	Con ayuda	*De forma independiente*
1. Alimentarse (si es preciso trocear la comida = ayuda)	5	10
2. Pasar de la silla de ruedas a la cama y volver a la silla (implica poder sentarse en la cama)	5-10	15
3. Aseo personal (lavarse la cara, peinarse, afeitarse, cepillarse los dientes)	0	5
4. Sentarse en el inodoro y levantarse (manejar la ropa, limpiarse, tirar de la cadena)	5	10
5. Lavarse	0	5
6. Caminar sobre una superficie plana (o bien impulsar la silla de ruedas, si es incapaz de caminar) *Solamente se debe puntuar si el paciente es incapaz de caminar	10 0*	15 5*
7. Subir y bajar escaleras	5	10
8. Vestirse (incluye atarse los cordones de los zapatos, cerrar cremalleras, broches y otros cierres)	5	10
9. Control de las deposiciones	5	10
10. Control de la micción	5	10

Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. Md State Med J 1965;14:61–5.

Annex 7. Dyspnoea scale mMRC (modified Medical Research Council)

Grade	Severity of symptom
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 metres or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest. 1988 Mar;93(3):580-6. doi: 10.1378/chest.93.3.580. PMID: 3342669.

Annex 8 Calculation of PaO2 from SpO2

It will be necessary to evaluate the PaO2/FiO2 ratio, to discriminate between 'Moderate' and 'Severe' categories, according to FDA guidance.

As most patients will only have determinations of oxyhemoglobin percent saturation with a pulse oximeter (SpO2), it will be necessary to implement a method for the estimation of the PaO2/FiO2 ratio to evaluate disease severity.

The Ellis inversion of the Severinghaus equation provides a useful nonlinear method for imputing PaO2 from SaO2. This technique has been used in cohorts of mostly nonintubated patients with pneumonia (3-5) and in patients with acute respiratory distress syndrome (6).

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

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

Ellis solution for the Severinghaus equation
(S= SpO_2 from pulse oximetry)

References

1. *Ellis R.K. Determination of Po2 from saturation. J Appl Physiol. 1989;67(2):902.*
2. *Severinghaus J.W. Simple, accurate equations for human blood O2 dissociation computations. J Appl Physiol. 1979;46(3):599-602.*
3. *Lanspa M.J., Jones B.E., Brown S.M., Dean N.C. Mortality, morbidity, and disease severity of patients with aspiration pneumonia. J Hosp Med. 2013;8(2):83-90.*
4. *Dean N.C., Jones J.P., Aronsky D. Hospital admission decision for patients with community-acquired pneumonia: variability among physicians in an emergency department. Ann Emerg Med. 2012;59(1):35-41.*
5. *Brown S.M., Jones B.E., Jephson A.R., Dean N.C., Infectious Diseases Society of America/American Thoracic Society Validation of the Infectious Diseases Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. Crit Care Med. 2009;37(12):3010-3016.*
6. *Brown SM, Grissom CK, Moss M, et al. Nonlinear Imputation of Pao2/Fio2 From Spo2/Fio2 Among Patients With Acute Respiratory Distress Syndrome. Chest. 2016;150(2):307-313. doi:10.1016/j.chest.2016.01.003*

Annex 9 Instructions for the 6 minute walk test.

See article and erratum in separate documents.

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002 Jul 1;166(1):111-7. doi: 10.1164/ajrccm.166.1.at1102. Erratum in: Am J Respir Crit Care Med. 2016 May 15;193(10):1185. PMID: 12091180.

APPENDIX

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters

Weight: _____ lbs, _____kg Blood pressure: _____ / _____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____ (Borg scale)
Fatigue	____	____ (Borg scale)
SpO_2	____ %	____%

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ____ (×60 meters) + final partial lap: _____ meters =

Total distance walked in 6 minutes: _____ meters

Predicted distance: _____ meters Percent predicted: _____%

Tech comments: