APL-D-003-20

# A Phase 3, Multicentre, Randomised, Controlled Trial to Determine the Efficacy and Safety of Two Dose Levels of Plitidepsin Versus Control in Adult Patients Requiring Hospitalisation for Management of Moderate COVID-19 Infection

STATISTICAL ANALYSIS PLAN

INVESTIGATIONAL MEDICINAL PRODUCTS: Plitidepsin

Protocol No: APL-D-003-20

EudraCT No: 2020-005951-19

NCT Code: NCT04784559

Version: v4.0

Date: including amendments #1 dated 28 May 2020, #2 dated 20 December 2021, #3 dated 01 July 2022 and #4 dated 21 April 2023.

## 16.1.9. Documentation of Statistical Methods

### 16.1.9.1. Statistical Analysis Plan

# Statistical Analysis Plan Addendum and TFL Mock Shells

## A Phase 3, Multicentre, Randomised, Controlled Trial to Determine the Efficacy and Safety of Two Dose Levels of Plitidepsin Versus Control in Adult Patients Requiring Hospitalisation for Management of Moderate COVID-19 Infection

Statistical Analysis Plan Addendum: Final
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Fortrea Study ID: 000000213894
Sponsor: Pharma Mar S.A.

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## Reviewers

The following reviews of the Statistical Analysis Plan (SAP) addendum were conducted:

| Name and Title | Role | Version Last Reviewed | Company / Organization |
|---|---|---|---|
| Mark Senior | Senior Biostatistician | Internal Draft v0.1 | Fortrea |
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## Glossary of Abbreviations

| Abbreviation | Term |
|---|---|
| DBL | DataBase Lock |
| SAP | Statistical Analysis Plan |
| TFLs | Tables, Figures and Listings |

# 1. Introduction

This SAP addendum consists of derivations and mocks for the post-hoc table, figure, and listing (TFL) shells. The TFLs presented in this document are mock-ups and may be subject to minor format modifications once the actual data are used. The data represented in this document are used for example purposes only and do not reflect the actual study data captured. The overall contents in any individual TFL shell are unlikely to change, although additional tables may be added if necessary, thus changing the table number scheme. Significant changes will need be approved by Fortrea and communicated to the Sponsor.

This document should be used in conjunction with the source documents described in Section 2, and serves as providing additional information to those documents, e.g., visit windows, baseline definitions etc. are described in the SAP version 4.0, and reviewers should reference that for further information.

The database lock (DBL) occurred on 26th April 2023, the mockshells specified in this document will be produced after DBL.

## 2. Source documents

This SAP addendum was written based on the following documentation:

| Document | Date | Version |
|---|---|---|
| Neptuno-APL-D-003-20 SAP | 21Apr2023 | 4.0 |
| Neptuno-APL-D-003-20 TFL Mock shells | 21Apr2023 | 4.0 |

## 3. TFL mock shells

For those outputs already described in the SAP and TFL mock shells version 4.0, the updates have been highlighted in red.

**Table 14.1.2.1.1 Post-hoc Analysis: Summary of Demographic Characteristics (Intent-To-Treat Population)**

| Characteristic<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) | Total<br>(N=XXX) |
|---|---|---|---|---|
| Age (years) | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Age Group (years), n (%) | | | | |
| >= 18 to 39 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 40 to 64 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 65 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Age Group (years), n (%) | | | | |
| >= 18 to 59 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 60 to 64 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 65 to 69 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 70 to 74 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 75 to 79 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 80 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Sex, n (%) | | | | |
| Male | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Female | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| … | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
[a] Only females. Percentages are calculated based on the number of females per group as the denominator.
[b] Patients with more than one race reported has been included in the Multiple category.
[c] Body mass index (kg/m^2) = body weight (kg) / height (m^2)
[d] Body surface area (m^2) = weight^0.425 (kg) × height^0.725 (cm) × 0.007184
Reference: Listing 16.2.4.1 and 16.2.4.2

*Programming notes (not part of the table):*

- *Table template TDM001.*
- *Include all parameters detailed in Table 14.1.2.1.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *A "Missing" category should only be presented under the subcategories for any categorical variable in case of missing data.*

The below tables are a repeat of table 14.1.2.1.1 Post-hoc:

**Table 14.1.2.1.2 Post-hoc Analysis: Summary of Demographic Characteristics - Patients who did not Achieve a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who did not achieve a sustained withdrawal of oxygen supplementation.*

**Table 14.1.2.1.3 Post-hoc Analysis: Summary of Demographic Characteristics - Patients who Achieved a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who achieved a sustained withdrawal of oxygen supplementation.*

**Table 14.1.2.1.4 Post-hoc Analysis: Summary of Demographic Characteristics - Patients from Site ES40 (Intent-To-Treat Population)**

- *Include only patients from site ES40.*

**Table 14.1.2.1.5 Post-hoc Analysis: Summary of Demographic Characteristics - All Patients Except Those from Site ES40 (Intent-To-Treat Population)**

- *Include all patients Except Those from site ES40.*

**Table 14.1.3.1.1 Post-hoc Analysis: Summary of Baseline Characteristics (Intent-To-Treat Population)**

| Characteristic<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) | Total<br>(N=XXX) |
|---|---|---|---|---|
| Chest Imaging at Enrolment, n (%) | | | | |
| Pulmonary Infiltrates | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Pleural Fluid | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Atelectasis | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Pulmonary Oedema | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Bilateral Pneumonia | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Lateral Pneumonia | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Other | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Periods of inclusion, n (%) | | | | |
| Beginning of accrual - August 2021 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| September 2021 - March 2022 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| April 2022 - End of accrual | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| *<continue for the following characteristics: Systolic Blood Pressure (mmHg) at Screening, Diastolic Blood Pressure (mmHg) at Screening, pulse rate (beats/min) at Screening, temperature (C) at Screening, respiration rate (breaths/min) at Screening, oxygen saturation ~~at room air~~ (%) at Screening and FiO2 (%) at Screening>* | | | | |
| Vaccination Status, n (%) | | | | |
| Fully Vaccinated | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Non-Fully Vaccinated | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| No Vaccinated | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Fully Vaccinated+ Non-Fully Vaccinated | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Reference: Listing 16.2.4.2

*Programming notes (not part of the table):*

- *Table template TDM002.*
- *Include all parameters detailed in Table 14.1.3.1.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

- *A "Missing" category should only be presented under the subcategories for any categorical variable in case of missing data.*

*Note: "at room air" have been removed from 'Oxygen saturation" label as it is not applicable in Tables 14.1.3.1, 14.3.5.1, 14.3.5.2 and Listing 16.2.4.2.*

The below tables are a repeat of table 14.1.3.1.1 Post-hoc:

**Table 14.1.3.1.2 Post-hoc Analysis: Summary of Baseline Characteristics - Patients who did not Achieve a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who did not achieve a sustained withdrawal of oxygen supplementation.*

**Table 14.1.3.1.3 Post-hoc Analysis: Summary of Baseline Characteristics – Patients who Achieved a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who achieved a sustained withdrawal of oxygen supplementation.*

**Table 14.1.3.1.4 Post-hoc Analysis: Summary of Baseline Characteristics - Patients from Site ES40 (Intent-To-Treat Population)**

- *Include only patients from site ES40.*

**Table 14.1.3.1.5 Post-hoc Analysis: Summary of Baseline Characteristics - All Patients Except Those from Site ES40 (Intent-To-Treat Population)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.1.3.2:

**Table 14.1.3.2.1 Post-hoc Analysis: Active Medical History by System Organ Class and Grouped Preferred Term - Patients who did not Achieve a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who did not achieve a sustained withdrawal of oxygen supplementation.*

**Table 14.1.3.2.2 Post-hoc Analysis: Active Medical History by System Organ Class and Grouped Preferred Term - Patients who Achieved a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who achieved a sustained withdrawal of oxygen supplementation.*

**Table 14.1.3.2.3 Post-hoc Analysis: Active Medical History by System Organ Class and Grouped Preferred Term - Patients from Site ES40 (Intent-To-Treat Population)**

- *Include only patients from site ES40.*

**Table 14.1.3.2.4 Post-hoc Analysis: Active Medical History by System Organ Class and Grouped Preferred Term - All Patients Except Those from Site ES40 (Intent-To-Treat Population)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.1.3.3:

**Table 14.1.3.3.1 Post-hoc Analysis: Past Medical History by System Organ Class and Grouped Preferred Term - Patients who did not Achieve a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who did not achieve a sustained withdrawal of oxygen supplementation.*

**Table 14.1.3.3.2 Post-hoc Analysis: Past Medical History by System Organ Class and Grouped Preferred Term - Patients who Achieved a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who achieved a sustained withdrawal of oxygen supplementation.*

**Table 14.1.3.3.3 Post-hoc Analysis: Past Medical History by System Organ Class and Grouped Preferred Term - Patients from Site ES40 (Intent-To-Treat Population)**

- *Include only patients from site ES40.*

**Table 14.1.3.3.4 Post-hoc Analysis: Past Medical History by System Organ Class and Grouped Preferred Term - All Patients Except Those from Site ES40 (Intent-To-Treat Population)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.1.4.1:

**Table 14.1.4.1.1 Post-hoc Analysis: Summary of Prior Medications - Patients who did not Achieve a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who did not achieve a sustained withdrawal of oxygen supplementation.*

**Table 14.1.4.1.2 Post-hoc Analysis: Summary of Prior Medications - Patients who Achieved a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who achieved a sustained withdrawal of oxygen supplementation.*

**Table 14.1.4.1.3 Post-hoc Analysis: Summary of Prior Medications - Patients from Site ES40 (Intent-To-Treat Population)**

- *Include only patients from site ES40.*

**Table 14.1.4.1.4 Post-hoc Analysis: Summary of Prior Medications - All Patients Except Those from Site ES40 (Intent-To-Treat Population)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.1.5.1:

**Table 14.1.5.1.1 Post-hoc Analysis: Summary of Signs and Symptoms - Patients who did not Achieve a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who did not achieve a sustained withdrawal of oxygen supplementation.*

**Table 14.1.5.1.2 Post-hoc Analysis: Summary of Signs and Symptoms - Patients who Achieved a Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

- *Include only patients who achieved a sustained withdrawal of oxygen supplementation.*

**Table 14.1.5.1.3 Post-hoc Analysis: Summary of Signs and Symptoms - Patients from Site ES40 (Intent-To-Treat Population)**

- *Include only patients from site ES40.*

**Table 14.1.5.1.4 Post-hoc Analysis: Summary of Signs and Symptoms - All Patients Except Those from Site ES40 (Intent-To-Treat Population)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.2.3.2:

**Table 14.2.3.2.1 Post-hoc Analysis: Total Duration of Advanced Oxygen Support - Patients from Site ES40 (Full Analysis Set)**

- *Include only patients from site ES40.*

**Table 14.2.3.2.2 Post-hoc Analysis: Total Duration of Advanced Oxygen Support - All Patients Except Those from Site ES40 (Full Analysis Set)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.2.3.9.1:

**Table 14.2.3.9.1.1 Post-hoc Analysis: Patients who Require High-Flow Oxygen - Patients from Site ES40 (Full Analysis Set)**

- *Include only patients from site ES40.*
- *Remove geographical region from model and footnotes because it is Not Applicable due to all patients belong to the same category.*

**Table 14.2.3.9.1.2 Post-hoc Analysis: Patients who Require High-Flow Oxygen - All Patients Except Those from Site ES40 (Full Analysis Set)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.2.3.9.2:

**Table 14.2.3.9.2.1 Post-hoc Analysis: Patients who Require High-Flow Oxygen per Period - Patients from Site ES40 (Full Analysis Set)**

- *Include only patients from site ES40.*
- *Remove geographical region from model and footnotes because it is Not Applicable due to all patients belong to the same category.*

**Table 14.2.3.9.2.2 Post-hoc Analysis: Patients who Require High-Flow Oxygen per Period - All Patients Except Those from Site ES40 (Full Analysis Set)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.2.3.10.1:

**Table 14.2.3.10.1.1 Post-hoc Analysis: Patients who Require Non-invasive Mechanical Ventilation - Patients from Site ES40 (Full Analysis Set)**

- *Include only patients from site ES40.*
- *Remove geographical region from model and footnotes because it is Not Applicable due to all patients belong to the same category.*

**Table 14.2.3.10.1.2 Post-hoc Analysis: Patients who Require Non-invasive Mechanical Ventilation - All Patients Except Those from Site ES40 (Full Analysis Set)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.2.3.10.2:

**Table 14.2.3.10.2.1 Post-hoc Analysis: Patients who Require Non-invasive Mechanical Ventilation per Period - Patients from Site ES40 (Full Analysis Set)**

- *Include only patients from site ES40.*
- *Remove geographical region from model and footnotes because it is Not Applicable due to all patients belong to the same category.*

**Table 14.2.3.10.2.2 Post-hoc Analysis: Patients who Require Non-invasive Mechanical Ventilation per Period - All Patients Except Those from Site ES40 (Full Analysis Set)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.2.3.11.1:

**Table 14.2.3.11.1.1 Post-hoc Analysis: Patients who Require Invasive Mechanical Ventilation or ECMO - Patients from Site ES40 (Full Analysis Set)**

- *Include only patients from site ES40.*
- *Remove geographical region from model and footnotes because it is Not Applicable due to all patients belong to the same category.*

**Table 14.2.3.11.1.2 Post-hoc Analysis: Patients who Require Invasive Mechanical Ventilation or ECMO - All Patients Except Those from Site ES40 (Full Analysis Set)**

- *Include all patients Except Those from site ES40.*

The below tables are a repeat of table 14.2.3.11.2:

**Table 14.2.3.11.2.1 Post-hoc Analysis: Patients who Require Invasive Mechanical Ventilation or ECMO per Period - Patients from Site ES40 (Full Analysis Set)**

- *Include only patients from site ES40.*
- *Remove geographical region from model and footnotes because it is Not Applicable due to all patients belong to the same category.*

**Table 14.2.3.11.2.2 Post-hoc Analysis: Patients who Require Invasive Mechanical Ventilation or ECMO per Period - All Patients Except Those from Site ES40 (Full Analysis Set)**

- *Include all patients Except Those from site ES40.*

**Table 14.2.4.1.1 Post-hoc Analysis: Time to Sustained Withdrawal of Oxygen Supplementation - Multivariate Analysis (Intent-To-Treat Population)**

| Variable | Parameter Estimate | Standard Error | p-value | Hazard Ratio |
|---|---|---|---|---|
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |

Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

If the patient is discontinued between day 15 and day 31 visits, and there is an attempt of contact and study discontinuation on or after the day 31 visit due date, the patient is censored at day 31.
[a] Parameter Estimate, Standard Error, p-value, and Hazard Ratio based on a Cox proportional-hazards regression model with treatment group, randomisation stratification factors, ie, geographical region (Europe, Rest of the World), Charlson Comorbidity Index (0 - 1, > 1) and pre-baseline Barthel index (≥ 90 versus < 90) as derived using the eCRF data, and patients included before and after amendment (Protocol v.6 or before, Protocol v.7), sex (female, male), age at study entry (18 to 39, 40 to 64, ≥ 65 years), race (asian, black, white, other), ethnic group (Hispanic or Latino, Not Hispanic or Latino), site location (Site XXX, Site XXX, Other Sites), ~~use of antiviral therapies or immunomodulatory drugs through the study (Yes, No),~~ previous COVID-19 vaccination status (Fully vaccinated + Non-fully vaccinated~~Fully vaccinated, Non-fully vaccinated~~, No vaccinated), anti-SARS-CoV-2 IgG at Day 1 (Non-positive, Positive), pre-randomisation dexamethasone (Yes, No), ~~total duration of corticoid therapy (< 9 days, [9 – 11] days, > 11 days), total cumulative dose of corticoid therapy (dexamethasone or equivalent) (≤ 60 mg, > 60 mg),~~ SARS-CoV-2 viral load (log10 copies/mL) at Day 1 before study drug administration (< 4, [4 - 7], > 7), time between onset date of COVID-19 symptoms and initiation of study treatment (≤ 5 days, 6 - 10 days, > 10 days), body mass index (kg/m2) at Screening (< 30, ≥ 30), hypertension at Screening (Yes, No), myocardial infarction (Yes, No), congestive heart failure (Yes, No), peripheral vascular disease (Yes, No), cerebrovascular disease (Yes, No), dementia (Yes, No), chronic obstructive pulmonary disease (Yes, No), connective tissue disease (Yes, No), peptic ulcer disease (Yes, No), liver disease (None, Mild, Moderate or Severe), diabetes mellitus (None or diet controlled, Uncomplicated, End-organ damage), hemiplegia (Yes, No), moderate or severe chronic kidney disease (Yes, No), solid tumor (None, Localized, Metastatic), leukemia (Yes, No), lymphoma (Yes, No), AIDS (Yes, No), ISARIC-4C mortality score (Low (0 - 3), Intermediate (4 - 8), High (9 - 14), Very high (≥ 15)), ISARIC-4C deterioration probability (≤ 25, (25 - 50], > 50), LDH at Baseline (≤ ULN, > ULN), CRP (mg/L) at Baseline (≤ 100, > 100), D-dimer at Baseline (≤ ULN, > ULN), ferritin at Baseline (≤ ULN, > ULN), creatinine at Baseline (≤ ULN, > ULN), IL-6 at Baseline (≤ Median, > Median), IL-10 at Baseline (≤ Median, > Median), lymphocytes count decreased at Baseline (Grade 0, Grade ≥ 1), neutrophils/lymphocytes ratio at Baseline (< 6, ≥ 6) and SARS-CoV-2 variant (Alpha, Beta, Gamma, Delta, Eta, Iota, Kappa, Lambda, Mu, any potential new variant) as covariates. Those covariates with more than 10% of missing values are omitted. A stepwise selection model is used, with significant level equal to 0.2 and 0.05, to enter into the model and to remain in the model, respectively.

*Programming notes (not part of the table):*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Omit those covariates with more than 10% of missing values from the multivariate analysis.*
- *Force to include the treatment arm in addition to the significant covariates.*
- *Remove the antiviral/immunomodulatory drug intake (no, yes), cumulative dose of corticoid therapy (≤60 mg, >60 mg) and total duration of corticoid therapy (<9 days, 9 to 11 days) variables from the modelling and the footnote.*

The below tables are a repeat of table 14.2.4.1:

**Table 14.2.4.1.2 Post-hoc Analysis: Time to Sustained Withdrawal of Oxygen Supplementation - Multivariate Analysis using a Random Forest Approach (Intent-To-Treat Population)**

| Variable | Parameter Estimate | Standard Error | p-value | Hazard Ratio |
|---|---|---|---|---|
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |

Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

If the patient is discontinued between day 15 and day 31 visits, and there is an attempt of contact and study discontinuation on or after the day 31 visit due date, the patient is censored at day 31.
[a] Parameter Estimate, Standard Error, p-value, and Hazard Ratio based on a Cox proportional-hazards regression model with treatment group, and Baseline IL-10 (continuous) as covariates.

*Programming notes (not part of the table):*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Force to include the treatment arm in addition to the covariates.*
- *Include the prognosis factors identified by Pharma Mar using a random forest approach as covariates in the modelling and the footnote.*

**Table 14.2.4.2.1 Post-hoc Analysis: Time to Sustained Hospital Discharge - Multivariate Analysis (Intent-To-Treat Population)**

| Variable | Parameter Estimate | Standard Error | p-value | Hazard Ratio |
|---|---|---|---|---|
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |

Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient

i. discharges from the hospital, and
ii. has no subsequent re-admission

If the patient is discontinued between day 15 and day 31 visits, and there is an attempt of contact and study discontinuation on or after the day 31 visit due date, the patient is censored at day 31.
[a] Parameter Estimate, Standard Error, p-value, and Hazard Ratio based on a Cox proportional-hazards regression model with treatment group, randomisation stratification factors, ie, geographical region (Europe, Rest of the World), Charlson Comorbidity Index (0 - 1, > 1) and pre-baseline Barthel index (≥ 90 versus < 90) as derived using the eCRF data, and patients included before and after amendment (Protocol v.6 or before, Protocol v.7), sex (female, male), age at study entry (18 to 39, 40 to 64, ≥ 65 years), race (asian, black, white, other), ethnic group (Hispanic or Latino, Not Hispanic or Latino), site location (Site XXX, Site XXX, Other Sites), ~~use of antiviral therapies or immunomodulatory drugs through the study (Yes, No),~~ previous COVID-19 vaccination status (Fully vaccinated + Non-fully vaccinated,~~Fully vaccinated, Non-fully vaccinated~~ No vaccinated), anti-SARS-CoV-2 IgG at Day 1 (Non-positive, Positive), pre-randomisation dexamethasone (Yes, No), ~~total duration of corticoid therapy (< 9 days, [9 – 11] days, > 11 days), total cumulative dose of corticoid therapy (dexamethasone or equivalent) (≤ 60 mg, > 60 mg),~~ SARS-CoV-2 viral load (log10 copies/mL) at Day 1 before study drug administration (< 4, [4 - 7], > 7), time between onset date of COVID-19 symptoms and initiation of study treatment (≤ 5 days, 6 - 10 days, > 10 days), body mass index (kg/m2) at Screening (< 30, ≥ 30), hypertension at Screening (Yes, No), myocardial infarction (Yes, No), congestive heart failure (Yes, No), peripheral vascular disease (Yes, No), cerebrovascular disease (Yes, No), dementia (Yes, No), chronic obstructive pulmonary disease (Yes, No), connective tissue disease (Yes, No), peptic ulcer disease (Yes, No), liver disease (None, Mild, Moderate or Severe), diabetes mellitus (None or diet controlled, Uncomplicated, End-organ damage), hemiplegia (Yes, No), moderate or severe chronic kidney disease (Yes, No), solid tumor (None, Localized, Metastatic), leukemia (Yes, No), lymphoma (Yes, No), AIDS (Yes, No), ISARIC-4C mortality score (Low (0 - 3), Intermediate (4 - 8), High (9 - 14), Very high (≥ 15)), ISARIC-4C deterioration probability (≤ 25, (25 - 50], > 50), LDH at Baseline (≤ ULN, > ULN), CRP (mg/L) at Baseline (≤ 100, > 100), D-dimer at Baseline (≤ ULN, > ULN), ferritin at Baseline (≤ ULN, > ULN), creatinine at Baseline (≤ ULN, > ULN), IL-6 at Baseline (≤ Median, > Median), IL-10 at Baseline (≤ Median, > Median), lymphocytes count decreased at Baseline (Grade 0, Grade ≥ 1), neutrophils/lymphocytes ratio at Baseline (< 6, ≥ 6) and SARS-CoV-2 variant (Alpha, Beta, Gamma, Delta, Eta, Iota, Kappa, Lambda, Mu, any potential new variant) as covariates. Those covariates with more than 10% of missing values are omitted. A stepwise selection model is used, with significant level equal to 0.2 and 0.05, to enter into the model and to remain in the model, respectively.

*Programming notes (not part of the table):*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Omit those covariates with more than 10% of missing values from the multivariate analysis.*
- *Force to include the treatment arm in addition to the significant covariates.*
- *Remove the antiviral/immunomodulatory drug intake (no, yes), cumulative dose of corticoid therapy (≤60 mg, >60 mg) and total duration of corticoid therapy (<9 days, 9 to 11 days) variables from the modelling and the footnote.*

**Table 14.2.5.1 Post-hoc Analysis: Clinical Status [0 - 2] in 11-point WHO Clinical Progression Scale (Full Analysis Set)**

| 11-point WHO Clinical Progression Scale | Plitidepsin 2.5mg (N=XXX) n (%) | Plitidepsin 1.5mg (N=XXX) n (%) | Control Arm (N=XXX) n (%) |
|---|---|---|---|
| Clinical Status [0 - 2] at Day 4 | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Clinical Status [0 - 2] at Day 8 | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Clinical Status [0 - 2] at Day 15 | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Clinical Status [0 - 2] at Day 31 | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator.
Notes: 11-point WHO Clinical Progression Scale, where 0= uninfected, no viral RNA detected; 1 = asymptomatic, viral RNA detected; 2 = symptomatic, independent; 3 = symptomatic, assistance needed; 4 = hospitalised, no oxygen therapy (if hospitalised for isolation only, record status as for ambulatory patient); 5 = hospitalised, oxygen by mask or nasal prongs; 6 = hospitalised, oxygen by NIV or high flow; 7 = intubation and mechanical ventilation, pO2/FIO2 ≥150 or SpO2/FIO2 ≥200; 8 = mechanical ventilation, pO2/FIO2<150 (SpO2/FIO2 <200) or vasopressors; 9 = mechanical ventilation, pO2/FIO2<150 and vasopressors, dialysis or ECMO; 10 = dead.
If the 11-point WHO scale at Discharge is assessed on the same date as the Day 8 visit, the 11-point WHO scale assessment at Discharge is used.
Otherwise, if an unscheduled assessment is also collected on the same date of the Day 8 visit, the worst 11-point WHO score is used.
Reference: Listing 16.2.6.1

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.5.2 Post-hoc Analysis: Time to Initiation with Immune-modulating Drugs (Intent-To-Treat Population)**

| Variable<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Patients who were Treated with Immune-modulating Drugs, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time to initiation with immune-modulating drugs (days) [a] | | | |
| n | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx |

N = number of patients in analysis set; n = number of patients in each category or with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
[a] Time to initiation with immune-modulating drugs (days) = (first day on which a patient receives subsequent immune-modulating drugs – date of randomisation).
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.3.1.1.1 Post-hoc Analysis: Summary of Corticoid Therapy (As Treated Population)**

| Variable<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Total Duration of Corticoid Therapy (days) | | | |
| n | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx |
| Total Duration of Corticoid Therapy (days), n (%) | | | |
| < 9 days | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| [9 - 11] days | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| > 11 days | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Total Cumulative Dose of Corticoid Therapy (mg) [a] | | | |
| n | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx |
| Total Cumulative Dose of Corticoid Therapy (mg) [a], n (%) | | | |
| <=60 mg | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| >60 mg | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |

N = number of patients in analysis set; n = number of patients in each category or with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
[a] in dexamethasone base equivalents.
Reference: Listing 16.2.4.5 and 16.2.5.2

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

The below tables are a repeat of table 14.3.1.1.1 Post-hoc:

**Table 14.3.1.1.2 Post-hoc Analysis: Summary of Corticoid Therapy - Patients who did not Achieve a Sustained Withdrawal of Oxygen Supplementation (As Treated Population)**

- *Include only patients who did not achieve a sustained withdrawal of oxygen supplementation.*

**Table 14.3.1.1.3 Post-hoc Analysis: Summary of Corticoid Therapy - Patients who Achieved a Sustained Withdrawal of Oxygen Supplementation (As Treated Population)**

- *Include only patients who achieved a sustained withdrawal of oxygen supplementation.*

**Table 14.3.1.1.4 Post-hoc Analysis: Summary of Corticoid Therapy - Patients from Site ES40 (As Treated Population)**

- *Include only patients from site ES40.*

**Table 14.3.1.1.5 Post-hoc Analysis: Summary of Corticoid Therapy - All Patients Except Those from Site ES40 (As Treated Population)**

- *Include all patients Except Those from site ES40.*

The below listing is a repeat of listing 16.2.7.1:

**Listing 16.2.7.5 Post-hoc Analysis: Adverse Events Considered as Nosocomial Infections Using the Wider Definition (Full Analysis Set)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Nosocomial Infection Type/ System Organ Class/ Grouped Preferred Term/ Verbatim | Start Date (Day)/ Stop Date (Day) [b]/ Duration (Days) or Ongoing | TEAE [c] | Severity/ Seriousness criteria | Relationship to Study Treatment | Action taken to Plitidepsin/ Dexamethasone/ Antiviral Control Arm [d] | Outcome |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxx/<br>xxxxxxxxxxx/<br>xxxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX | | Grade X/<br>xxxxxx | xxxxxxxxxxx | xxxxxxxxxxxxx/<br>xxxxxxxxxxxxx/<br>xxxxxxxxxxxxx | xxxxxxxxxxx |
| 123-456789 | 45/M/W | Musculoskeletal and connective tissue disorders/<br>Periarthritis/<br>Shoulder Periarthritis(Both) | 14AUG2018 (82)/<br>24AUG2018 (61)/<br>15 | * | Grade 5/<br>Death | No - Study disease | Not Applicable/<br>Dose not Changed/<br>Dose not Changed | Fatal |
| etc. | | | | | | | | |

Note: The wider definition also considers AEs with SOC term 'Infections and infestations' that are discussed with the medical monitor and defined according to Centers for Disease Control and Prevention's health care associated infection definition (Horan TC et al).
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] TEAE=Treatment Emergent Adverse Event. TEAEs are flagged with *.
[d] Antiviral control arm is the regulatory-approved antiviral for those patients randomised to the control arm, i.e., remdesivir or favipiravir.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE001.*
- *Order by Site ID - Patient ID and AE No.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *Nosocomial Infections using the wider definition are those AEs with ADAE.NOSOCOFL = Y.*
- *Nosocomial Infection Type is the "Column C" from the "Neptuno_Nosocomial Infections_13March2023_updated by IM_25Apr2023_final.xlsx" file, and it must be presented as*
  - *Bloodstream Infection (for Column C = BSI)*
  - *Eye, Ear, Nose, Throat, or Mouth Infection (for Column C = EENT)*
  - *Lower Respiratory Tract Infection, Other than Pneumonia (for Column C = LRI)*

- *Pneumonia (for Column C = PNEU)*
- *Skin and Soft Tissue Infection (for Column C = SST)*
- *Urinary Tract Infection (for Column C = UTI)*

The below figures are a repeat of figure 14.2.1.1:

**Figure 14.2.1.1.1 Post-hoc Analysis: Time to Sustained Withdrawal of Oxygen Supplementation, Plitidepsin 2.5 mg Vs Control Arm - Kaplan-Meier Plot (Intent-To-Treat Population)**

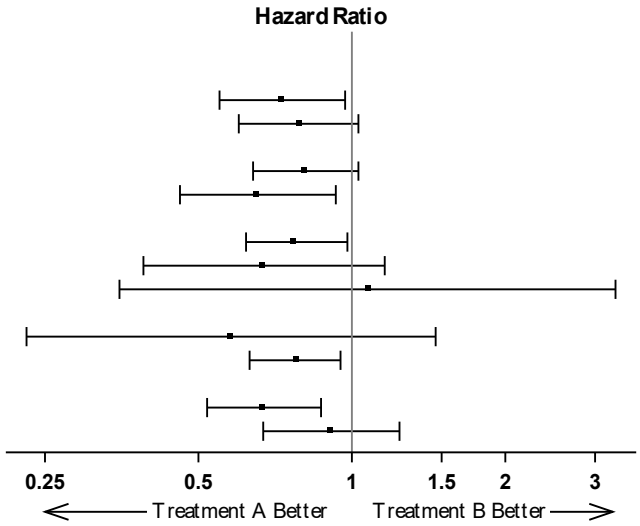
- *Include only patients in Plitidepsin 2.5 mg or Control Arm.*

**Figure 14.2.1.1.2 Post-hoc Analysis: Time to Sustained Withdrawal of Oxygen Supplementation, Plitidepsin 1.5 mg Vs Control Arm - Kaplan-Meier Plot (Intent-To-Treat Population)**

- *Include only patients in Plitidepsin 1.5 mg or Control Arm.*

**Figure 14.2.1.2.1 Post-hoc Analysis: Time to Sustained Withdrawal of Oxygen Supplementation - Subgroup Analysis - Forest Plot (Intent-To-Treat Population)**

| Subgroup | Treatment A N | Treatment B N | HR (95% CI) |
|---|---|---|---|
| **Age (years)** | | | |
| <65 | 1077 | 1091 | 0.73 (0.55, 0.97) |
| ≥65 | 862 | 846 | 0.79 (0.60, 1.03) |
| **Gender** | | | |
| Male | 1293 | 1245 | 0.81 (0.64, 1.03) |
| Female | 646 | 692 | 0.65 (0.46, 0.93) |
| **Race** | | | |
| White | 1600 | 1619 | 0.77 (0.62, 0.98) |
| Black or African American | 218 | 225 | 0.67 (0.39, 1.16) |
| Other | 88 | 60 | 1.08 (0.35, 3.29) |
| **Ethnicity** | | | |
| Hispanic or Latino | 75 | 72 | 0.58 (0.23, 1.46) |
| Not Hispanic | 1852 | 1857 | 0.78 (0.63, 0.95) |
| **Body Mass Index** | | | |
| < 30 | 1123 | 1096 | 0.67 (0.52, 0.87) |
| ≥ 30 | 810 | 835 | 0.91 (0.67, 1.24) |



*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Forest Plot |
| Figure Template ID | FG006 |
| Treatment display details | Display 2 treatment groups per page. Plitidepsin 2.5mg vs Control Arm on page 1 and Plitidepsin 1.5mg vs Control Arm on page 2. |
| X-axis label | <---------- Control Arm Better Plitidepsin 2.5mg Better ---------> on page 1.<br><---------- Control Arm Better Plitidepsin 1.5mg Better ---------> on page 2. |
| X-axis Scale | 0.33; 0.5; 0.66; 1; 1.5; 2; 3. |
| Y-axis label | Nil. |
| Y-axis Scale | Major tick: Nil>>, Minor tick: Nil. |
| Legend | Display 2 treatment groups per page.<br>Subgroup Plitidepsin 2.5mg N Control Arm N HR [b] (95% CI) Hazard Ratio (on page 1)<br>Subgroup Plitidepsin 1.5mg N Control Arm N HR [b] (95% CI) Hazard Ratio (on page 2) |
| Legend position | Top |
| Annotations | Include reference line |
| Other notes | Display subgroups as following:<br>All patients<br>Charlson Comorbidity Index<br>0 - 1<br>> 1<br>Geographical Region<br>Europe<br>Rest of the World<br>Pre-baseline Barthel index<br>≥ 90<br>< 90<br>Patients included before and after amendment<br>Protocol v.6 or before<br>Protocol v.7<br>Sex<br>Female<br>Male |

Age at study entry (years)
- 18 to 39
- 40 to 64
- ≥ 65

Race
- Asian
- Black
- White
- Other

Ethnic group
- Hispanic or Latino
- Not Hispanic or Latino

Site location: each study site with more than 1/6 out of the randomised patients (i.e. >33 randomised patients for the futility analysis and >101 randomised patients for the final analysis) will be considered as a group and the remaining study sites, i.e. those study sites with less than 1/6 out of the randomised patients will be pooled together as a one single group
- Site XXX
- Site XXX
- Other Sites

~~Use of antiviral therapies or immunomodulatory drugs through the study~~
- ~~Yes~~
- ~~No~~

Previous COVID-19 vaccination status
- Fully vaccinated
- Non-fully vaccinated
- No vaccinated
- Fully vaccinated + Non-fully vaccinated

Anti-SARS-CoV-2 IgG Day 1
- Non-positive
- Positive

Pre-randomisation dexamethasone
- Yes
- No

~~Total duration of corticoid therapy~~
- ~~< 9 days~~
- ~~[9 – 11] days~~
- ~~> 11 days~~

~~Total cumulative dose of corticoid therapy (dexamethasone or equivalent)~~
- ~~≤ 60 mg~~

~~> 60 mg~~
SARS-CoV-2 viral load (log10 copies/mL) at Day 1 before study drug administration
< 4
[4 - 7]
> 7
Time between onset date of COVID-19 symptoms and initiation of study treatment
≤ 5 days
6 - 10 days
> 10 days
Body mass index (kg/m2) at Screening
< 30
≥ 30
Hypertension at Screening
Yes
No
Myocardial infarction at Screening
Yes
No
Congestive heart failure at Screening
Yes
No
Peripheral vascular disease at Screening
Yes
No
Cerebrovascular disease at Screening
Yes
No
Dementia at Screening
Yes
No
Chronic obstructive pulmonary disease at Screening
Yes
No
Connective tissue disease at Screening
Yes
No
Peptic ulcer disease at Screening
Yes
No

Liver disease at Screening
- None
- Mild
- Moderate or Severe

Diabetes mellitus at Screening
- None or diet controlled
- Uncomplicated
- End-organ damage

Hemiplegia at Screening
- Yes
- No

Moderate or severe chronic kidney disease at Screening
- Yes
- No

Solid tumor at Screening
- None
- Localized
- Metastatic

Leukemia at Screening
- Yes
- No

Lymphoma at Screening
- Yes
- No

AIDS at Screening
- Yes
- No

ISARIC-4C mortality score
- Low (0 - 3)
- Intermediate (4 - 8)
- High (9 - 14)
- Vey high (≥ 15)

ISARIC-4C deterioration probability (%)
- ≤ 25
- (25 - 50]
- > 50

LDH at Baseline
- ≤ ULN
- > ULN

CRP (mg/L) at Baseline
- ≤ 100
- > 100

D-dimer at Baseline
- ≤ ULN
- > ULN

Ferritin at Baseline
- ≤ ULN
- > ULN

Creatinine at Baseline
- ≤ ULN
- > ULN

IL-6 at Baseline
- ≤ Median
- > Median

IL-10 at Baseline
- ≤ Median
- > Median

IL-10 at Baseline
- ≤ 3.8 ng/L
- > 3.8 ng/L

Lymphocytes count decreased at Baseline
- Grade 0
- Grade ≥ 1

Neutrophils/lymphocytes ratio at Baseline
- < 6
- ≥ 6

SARS-CoV-2 variant
- Alpha
- Beta
- Gamma
- Delta
- Eta
- Iota
- Kappa
- Lambda
- Mu
- <Any other potential new variant>

Display the following footnotes:

HR = Hazard Ratio; CI = Confidence Interval; AIDS = Acquired Immunodeficiency Syndrome.
Charlson Comorbidity and pre-baseline Barthel Index as derived using the eCRF data.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale).

[a] Hazard Ratio calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and the levels of the randomisation stratification factors, ie, geographical region, and Charlson Comorbidity Index and pre-baseline Barthel index as derived using the eCRF data as covariates, except that for the Charlson Comorbidity Index subgroup analysis, the randomisation stratum of Charlson Comorbidity Index will not be included as a covariate; for the Geographical Region subgroup analysis, the randomisation stratum of Geographical Region will not be included as a covariate; and for the pre-baseline Barthel index subgroup analysis, the randomisation stratum of pre-baseline Barthel index will not be included as a covariate.

*Programming notes (not part of the table):*

- *Remove the antiviral/immunomodulatory drug intake (no, yes), cumulative dose of corticoid therapy (≤60 mg, >60 mg) and total duration of corticoid therapy (<9 days, 9 to 11 days) subgroups.*

The below figures are a repeat of figure 14.2.2.1:

**Figure 14.2.2.1.1 Post-hoc Analysis: Time to Sustained Hospital Discharge, Plitidepsin 2.5 mg Vs Control Arm - Kaplan-Meier Plot (Intent-To-Treat Population)**

- *Include only patients in Plitidepsin 2.5 mg or Control Arm.*

**Figure 14.2.2.1.2 Post-hoc Analysis: Time to Sustained Hospital Discharge, Plitidepsin 1.5 mg Vs Control Arm - Kaplan-Meier Plot (Intent-To-Treat Population)**

- *Include only patients in Plitidepsin 1.5 mg or Control Arm.*

**Type of Approval (select one) :** ☐ **SAP** ☐ **Initiation of Programming SAP** ☒ **SAP Addendum**

| | | | |
|---|---|---|---|
| **Sponsor Name:** | **Pharma Mar S.A.** | | |
| **Sponsor Protocol/ CIP ID:** | **APL-D-003-20** | **Fortrea Study ID:** | **000000213894** |
| **SAP text filename:** | **Neptuno-APL-D-003-20_SAP Addendum and TFL shells_Final_v2.0_12Sep2023.docx** | | |
| **TFL shells filename:** | **Neptuno-APL-D-003-20_SAP Addendum and TFL shells_Final_v2.0_12Sep2023.docx** | | |
| **Version:** | **2.0** | **Date:** | **12Sep2023** |

## Fortrea Approval(s):

**Lead Statistician**

| | |
|---|---|
| **Approval Signature**<br>**Print Name**<br>**Date** | DocuSigned by Igor Martin<br>Igor Martin \| I am the author of this document<br>12 Sep 2023 \| 4:19:45 AM EDT<br>5C422D2049CC440F85DD6E151F20DC39 |

## Sponsor Approval(s):

By signing below when the SAP Addendum is considered final, the signatories agree to the additional analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP addendum has been signed any modifications made after signing may result in a work-scope change.

| | |
|---|---|
| **Approval Signature**<br>**Print Name**<br>**Date** | DocuSigned by Antonio Nieto Archilla<br>Antonio Nieto Archilla \| Apruebo este documento<br>12 sep. 2023 \| 4:23:38 AM EDT<br>C6ACB764EDC6417EBC6B6F84AE3BB8C8 |

Fortrea

# TMF File Note

| | | | |
|---|---|---|---|
| **Sponsor Name:** | Pharma Mar S.A. | **Fortrea Study ID :** | 000000213894 |
| **Sponsor Protocol/CIP No.:** | APL-D-003-20 | **Date** (dd mmm yyyy) | 03 Jul 2023 |
| **Investigator Name:** | NA | **Site No.:** | NA |
| **Artifact Name:** | 000000213894 Statistical Analysis Plan 21 Apr 2023<br>000000213894 Statistical Analysis Plan 24 Apr 2023 | **Artifact No:** | CVD-TMF-7706943<br>CVD-TMF-7706979 |
| **Topic :** | Inaccurate document date in Statistical Analysis Plan v4.0 and SAP text filename and the TFL shells filename in the corresponding SAP v4.0 approval form | | |

## Description:

**Artifact No: CVD-TMF-7706943 - 000000213894 Statistical Analysis Plan 21 Apr 2023**

Due to a mistake, the document date was not updated in the footer of the Statistical Analysis Plan (SAP) text version 4.0. The correct document date is 21 Apr 2023.

**Artifact No: CVD-TMF-7706979 - 000000213894 Statistical Analysis Plan 24 Apr 2023 (Approval Form)**

The SAP text filename and the TFL shells filename are not correct in the corresponding SAP v4.0 approval form. The correct SAP text filename and the TFL shells filename are:

SAP text filename: Neptuno-APL-D-003-20_SAP Final v4.0_21Apr2023
TFL shells filename: Neptuno-APL-D-003-20_SAP TFL Shells Final v4.0_21Apr2023

## Note to File completed by:

Igor Martín Rodríguez — Typed Name
03 Jul 2023 — Date (dd mmm yyyy)
Principal Statistician — Title

# Statistical Analysis Plan

# Pharma Mar S.A.

# Sponsor Protocol ID: APL-D-003-20

# A Phase 3, Multicentre, Randomised, Controlled Trial to Determine the Efficacy and Safety of Two Dose Levels of Plitidepsin Versus Control in Adult Patients Requiring Hospitalisation for Management of Moderate COVID-19 Infection

Labcorp Drug Development Study ID: 000000213894

Document Version: Final v4.0

Document Date: 21 Apr 2023

**Labcorp Drug Development**
**Clinical Development Commercialization Services**

# Table of Contents

# Reviewers

The following reviews of the SAP were conducted:

| Name and Title | Role | Version Last Reviewed | Company/ Organization |
|---|---|---|---|
| Ewa Kraszewska | Peer Review Statistician | Internal Draft v0.1 | Labcorp Drug Development |
| David Dolling | Peer Review Statistician | Internal Draft v2.1 | Labcorp Drug Development |
| Julija Jasauskiene | Lead Programmer | Internal Draft v0.1 | Labcorp Drug Development |
| Tahseen Khan | Medical Writer | Internal Draft v0.1 | Labcorp Drug Development |
| Weiqiang Wang | DMC Support statistician | Internal Draft v2.1 | Labcorp Drug Development |
| Elena Semenova | Lead Programmer | Draft v2.3 | Labcorp Drug Development |
| Ravi Venkataramana | Lead Programmer | Draft v3.2 | Labcorp Drug Development |
| Antonio Nieto | Bio Statistics Departamental Manager | Draft v3.2 | PharmaMar |
| Javier Gómez | Bio Statistics Departamental Senior Manager | Draft v3.2 | PharmaMar |
| Sonia Extremera | Bio Statistics Departamental Biostatician | Draft v3.2 | PharmaMar |

# Glossary of Abbreviations

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| ATC | anatomical therapeutic chemical |
| CI | confidence interval |
| CRP | C-reactive protein |
| COVID-19 | coronavirus disease 2019 |
| CPK | creatine phosphokinase |
| eCRF | electronic case report form |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| ECMO | extracorporeal membrane oxygenation |
| FAS | full analysis set |
| $FiO_2$ | fraction of inspired oxygen |
| GGT | gamma-glutamyltransferase |
| ICU | intensive care unit |
| IDMC | independent data monitoring committee |
| Ig | immunoglobulin |
| IL | interleukin |
| IRT | interactive response technology |
| ITT | intention-to-treat |
| IV | intravenous |
| LDH | lactate dehydrogenase |
| LLOQ | lower limit of quantification |
| LLT | lowest level terms |
| LOCF | last observation carried forward |
| LOD | limit of detection |
| LS | least squares |
| MedDRA | medical dictionary for regulatory activities |
| NIV | noninvasive ventilation |
| NLR | neutrophils/lymphocytes ratio |
| NRI | non-responder imputation |
| NT-pro-BNP | N-terminal pro b-type natriuretic peptide |
| PO | oral administration |
| $pO_2$ | partial pressure of oxygen |
| PP | per-protocol |
| PT | preferred term |
| qPCR | quantitative polymerase chain reaction |
| QTc | corrected QT interval |
| QTcF | Fridericia corrected QT interval |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAR | serious adverse reactions |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SD | standard deviation |

| | |
|---|---|
| SE | standard error |
| SMQ | standardised MedDRA query |
| SOC | system organ class |
| $SpO_2$ | saturation of oxygen |
| TEAE | treatment-emergent adverse event |
| TNFα | tumour necrosis factor alpha |
| TFLs | tables, figures and listings |
| ULN | upper limit of normal |
| WHO | World Health Organization |

# 1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

| Document | Date | Version |
|---|---|---|
| Protocol | 29MAR2022 | Final 7.0 |
| Electronic case report form (eCRF) | 27FEB2023 | 7.0 |
| IDMC Charter | 22APR2022 | Final 3.0 |

# 2. Protocol Details

## 2.1 Study Objectives

### 2.1.1 Primary Objective

The primary objective of this study is to compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control assessing the need of supplementary oxygen.

### 2.1.2 Key Secondary Objective

The key secondary objective of this study is to compare efficacy of plitidepsin 1.5 mg and 2.5 mg versus the control assessing the time to sustained hospital discharge.

### 2.1.3 Secondary Objectives

#### 2.1.3.1 Efficacy Secondary Objectives

The efficacy secondary objectives of this study are

- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control assessing clinical status by the 11-category World Health Organization (WHO) Clinical Progression Scale.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the need of advanced oxygen support.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the need for intensive care support.

#### 2.1.3.2 Safety Secondary Objectives

The safety secondary objectives of this study are

- To compare safety/tolerability of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of adverse events, adverse reactions and mortality.
- To compare safety/tolerability of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of abnormal laboratory parameters.
- To compare safety/tolerability of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of variations of vital signs.

- To compare safety/tolerability of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of ECG variations.

### 2.1.3.3 Other Secondary Objectives

The other efficacy secondary objectives of this study are

- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of hospital readmission related to COVID-19.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of clinical evolution.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the need of supplementary oxygen.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the need of intensification of respiratory or intensive care support.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the need of intensification of pharmacological therapies.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of superinfections.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of mortality.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the evolution of viral load.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the evolution of inflammatory markers.
- To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control in terms of the immune response against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- To compare efficacy in the primary endpoint and describe safety/tolerability of pooled plitidepsin arms versus control.
- To compare efficacy in the primary endpoint and describe safety/tolerability between plitidepsin arms (1.5 versus 2.5 mg) in case both are significantly superior to the control.
- To explore the influence of risk factors or scores for clinical deterioration that were not individually included.
- To compare the results obtained before and after the change of the primary and key secondary endpoint (protocol v.6 versus v.7).

## 2.2 Overall Study Design

This is a randomised, multicentre, open-label, controlled Phase 3 study in which adults requiring hospital admission and oxygen supplementation for management of moderate COVID-19 infection will be randomised in 1:1:1 to:

- Plitidepsin 1.5 mg arm: Patients will receive plitidepsin 1.5 mg/day intravenous (IV) in addition to dexamethasone on days 1 to 3;
- Plitidepsin 2.5 mg arm: Patients will receive plitidepsin 2.5 mg/day IV in addition to dexamethasone on days 1 to 3;
- Control arm: Patients will receive dexamethasone IV on Days 1 to 3. Additionally, in accordance with local treatment guidelines, patients in this group may receive a regulatory-approved antiviral treatment.

The study allows up to a total cumulative dose of 60 mg of dexamethasone base (calculation of the total dose will also include corticosteroids administered within 72 hours before the start of the study treatment and dexamethasone administered as premedication).

Randomisation will be stratified for 3 factors:

- Geographical region (Europe vs. Rest of the World);
- Charlson Comorbidity Index (0-1 vs. >1); and
- Barthel Index (≥90 versus <90)

From treatment initiation on Day 1, patients will be followed in the hospital for at least 4 days and then through Day 31 (±3 days) or resolution/stabilisation of treatment-related adverse events (AEs), treatment-emergent adverse events (TEAEs) of special interest, and serious adverse events (SAEs). Patients discharged from the hospital prior to Day 8 will return to an out-patient clinic for assessments on Days 8 (±1 day), and 31 (±3 days). On Day 15 (±1 day), patients will be followed up in remote or on-site visit (Appendix 4).

An independent Data Monitoring Committee (IDMC) will oversee study conduct (safety and primary endpoint), including analysis of summary safety data as per the trial requirements.

The study is expected to randomise approximately 609 patients (203 in each arm) over a period of 20 months.

Patients will be considered to be on study from the signature of the informed consent form until the end of the follow-up period, that is, completion of the protocol-specified follow-up visit on Day 31 (±3 days) or until resolution/ stabilisation of treatment-related AEs, TEAEs of special interest, and SAEs that occurred through Day 31, whichever is longer.

Additionally, a dedicated corrected QT interval (QTc) substudy will be performed in a subset of approximately 50 patients with electrocardiogram (ECG) collected over Days 1 to 3 using Holter monitors to assess treatment impact on QTc prolongation.

## 2.3 Sample Size and Power

A total sample size of 609 patients (203 in each arm) with 530 events necessary for the analysis of the primary endpoint has been calculated based on a 1-sided type I error rate of 1.25% ($\alpha = 0.0125$) with at least 80% power ($\beta = 0.2$) to detect target hazard ratio (HR) of 1.4 in the time to sustained withdrawal of supplementary oxygen, which means a decrease in the median time to the event from 8 days (control arm) to 5.7 days (plitidepsin). This sample size is adjusted for the multiple comparisons of each plitidepsin arm with control group by a Bonferroni adjustment, although other advanced methods for correction of multiplicity will be used for the main analysis that will increase the power of the tests. At the final analysis, if HR is 1.27 or greater, in favour of any plitidepsin arm, (equivalent to a decrease in the median time to sustained withdrawal of supplementary oxygen of 1.7 days or greater), then it is expected that the null hypothesis (ie, HR≤1) will be rejected.

A futility analysis for efficacy/safety will be performed when 33% of events (sustained withdrawal of supplementary oxygen) have been reached. The rho family of beta-spending functions (with $\rho = 1.18$) will be used for the calculation of the stopping boundaries for futility in order to control type II error. The stopping boundaries for the futility analysis will be calculated with the actual number of events available in the Intent-To-Treat (ITT) population at that moment; if the number of events at the futility analysis is 116 events in a pair comparison, the beta spending corrected p-value to reject the alternative hypothesis should be higher or equal than 0.4199 and this p-value is associated with a HR≤1.0382.

At the futility analysis, once 33% of events of the planned 530 have been reached the conditional power will be calculated. As an example, if clinical trial design hypotheses are seen, a conditional power of 86.9% would be achieved for an interim test Z-statistic of 1.812 assuming the HR is 1.4 in favour of the plitidepsin arms (median time to the event of 5.7 for the plitidepsin arms compared with 8 days for the control arm) and a 1-sided analysis at the 1.25% significance level.

If the recommendation of the IDMC is to discontinue one of the plitidepsin dosing arms at this futility analysis following the stopping rules, the study will continue from that point on a 1:1 randomisation fashion until the completion of the remaining treatment arms (203 patients per arm and 353 events of sustained withdrawal of supplementary oxygen in total necessary to perform the final analysis). The patients still ongoing in the dropped arm would continue to be followed-up as per protocol and a Bonferroni-adjusted type I error rate of 1.25% will be kept for the comparison of the primary endpoint between the remaining plitidepsin arm and the control arm.

# 3. Efficacy and Safety Variables

## 3.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the time to sustained withdrawal of supplementary oxygen (11-category WHO Clinical Progression Scale ≤4) with no subsequent reutilisation during remaining study period.

## 3.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the time to sustained (ie, with no subsequent readmission to Day 31) hospital discharge (since randomisation).

## 3.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Clinical status by the 11-category WHO Clinical Progression Scale, at Day 8 (±1)
- Total duration of advanced oxygen support (high-flow nasal oxygen, extracorporeal membrane oxygenation [ECMO], non-invasive ventilation or mechanical ventilation).
- Percentage of patients in each study group requiring admission to intensive care unit (ICU) on Days 4, 8, 15 and 31.

## 3.4 Safety Variables

The safety/tolerability endpoints are as follows:

- Frequency of TEAEs, TEAEs ≥ grade 3 according to the National Cancer Institute-Common Terminology Criteria for AEs (NCI-CTCAE, version 5.0), TEAEs of special interest, serious TEAEs, serious treatment-related TEAEs, TEAEs leading to treatment discontinuation, and deaths.
- Actual and change from Baseline in clinical laboratory results.
- Actual and change from Baseline in vital signs results.
- Actual and change from Baseline in ECG findings.

## 3.5 Other Secondary Endpoints

The other secondary endpoints are:

- Percentage of patients in each study group who require hospital readmission related to COVID-19 through Day 31.
- Percentage of patients in each study group and in each of the categories of the 11-point WHO Clinical Progression Scale on Days 4, 8, 15 and 31.
- Percentage of patients in each study group requiring oxygen therapy on Days 4, 8, 15 and 31.
- Time to intensification of respiratory support (WHO >6 [intubation]).

- Total duration of ICU stay for each study group.
- Percentage of patients in each study group requiring high-flow oxygen on Days 4, 8, 15, and 31.
- Percentage of patients in each study group requiring non-invasive mechanical ventilation on Days 4, 8, 15 and 31.
- Percentage of patients in each study group requiring invasive mechanical ventilation or ECMO on Days 4, 8, 15, and 31.
- Time to initiation with immune-modulating drugs.
- Time to initiation with antiviral drugs.
- Percentage of patients receiving subsequent immune-modulating drugs on Days 4, 8, 15 and 31.
- Percentage of patients receiving subsequent antiviral drugs on Days 4, 8, 15 and 31.
- Percentage of patients in each study group with nosocomial infection by Days 4, 8, 15 and 31.
- Mortality in each study group on Days 4, 8, 15 and 31.
- Change in the viral load of SARS-CoV-2 in each study group from Day 1 before administration of the study drug until Day 8.
- Percentage of patients in each study group with undetectable viral load of SARS-CoV-2 on Day 8.
- Change in inflammatory biomarkers (C- reactive protein [CRP], ferritin, interleukin [IL]-6, IL-1β, IL-10 and tumour necrosis factor alpha [TNFα]) in each study group from baseline until Days 2, 3, 4, 8, and 31.
- Change respect to baseline in individual serological assessments.
- Time to sustained withdrawal of supplementary oxygen (11-category WHO Clinical Progression Scale ≤4) with no subsequent reutilisation during remaining study period, before (protocol v.6) and after the amendment (protocol v.7).
- Time to sustained (ie, with no subsequent readmission to Day 31) hospital discharge (since randomisation), before (protocol v.6) and after the amendment (protocol v.7).
- Obesity, hypertension, age and individual co-morbidities included in the Charlson Index (Appendix 11- Age-adjusted Charlson Index), ISARIC-4C score (Appendix 14 - ISARIC 4C Mortality & 4C Deterioration Scores), or vaccination status.

# 4. Pharmacokinetic/Pharmacodynamic variables

Patients participating in the QTc substudy will have blood sampling for PK assessments over Days 1 to 4.

The QTc substudy will be managed by a vendor (ERT - eResearchTechnology, Inc). The data analysis methods will be detailed in a separate statistical analysis plan and results will be reported separately.

# 5. Analysis Populations

Analysis of the primary, key secondary and other time-to-event efficacy endpoints will be performed in the ITT population. Other secondary efficacy endpoints will be based on the FAS population. A sensitivity analysis will be performed for the primary endpoint, key secondary and other time-to-event efficacy endpoints in the FAS population. Supportive analyses will be performed on the Per Protocol (PP) population. Safety endpoints analyses will be based on the As Treated population.

## 5.1 Intent-To-Treat (ITT) Population

The ITT will consist of all randomised patients, regardless of whether they received treatment. ITT patients are analysed according to their randomised treatment.

## 5.2 As Treated Population

All patients who received any exposure to any study drug (plitidepsin, dexamethasone, including for patients randomised to control arm, the regulatory-approved antiviral treatments, such as, remdesivir or favipiravir) during the study will be part of the As Treated population. As Treated population will be analysed according to the treatment they actually received.

## 5.3 Full Analysis Set (FAS)

The FAS will consist of all randomised patients who received at least 1 dose of any study drug (plitidepsin, dexamethasone, including for patients randomised to control arm, the regulatory-approved antiviral treatments, such as, remdesivir or favipiravir) during the study and with at least 1 post-baseline clinical status collected. FAS patients are analysed according to their randomised treatment.

## 5.4 Per Protocol (PP) Population

The PP population will consist of all patients in the FAS population who did not have any important protocol deviations that would interfere with the collection or interpretation of the efficacy. PP patients are analysed according to their randomised treatment.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Section 5.4.1 details the deviations.

| Category | Sub Category | Project Specific Protocol Deviation | Detection Method |
|---|---|---|---|
| Study Conduct/ Procedures | Inclusion/ Exclusion Criteria | Failure to complete or comply with inclusion/exclusion criteria | **Programmable/Non-programmable** |
| Study Conduct/ Procedures | Screening | Non-compliance with screening procedure protocol requirements to confirm eligibility of the patient | **Programmable/Non-programmable** |
| Study Conduct/ Procedures | Study Restrictions/ Withdrawal | Non-compliance with protocol restrictions (e.g. use of prohibited medication or prohibited treatment therapy) | **Non-programmable** Labcorp Drug Development will provide the medical monitor with the lists of prior and concomitant medications taken by patients. The medical monitor will review this list and note any prohibited medications or therapies. |
| Study Conduct/ Procedures | Dose Formulation/ Dose Administration | Administration Use of prohibited medication | **Non-programmable** Labcorp Drug Development will provide the medical monitor with the lists of prior and concomitant medications taken by patients. The medical monitor will review this list and note any prohibited medications or therapies. |

| Category | Sub Category | Project Specific Protocol Deviation | Detection Method |
|---|---|---|---|
| Study Conduct/ Procedures | Dose Formulation/ Dose Administration | Incorrect study drug dose, frequency, timing or method of drug delivery (e.g. subject overdosed with study drug, incomplete study drug administered), incorrect volume of infusion | **Programmable/Non-programmable** |
| Study Conduct/ Procedures | Dose Formulation/ Dose Administration | Study drug dosing adjustments performed outside of Protocol | **Programmable/Non-programmable** |

### 5.4.1 Important Protocol Deviations Leading to Exclusion from the PP Population Analysis

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the patients from the PP population. For the purposes of this study, the following criteria have been identified as important protocol deviations leading to exclusion from the PP population as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint.

As defined in the table, the majority of the important protocol deviations leading to exclusion from the PP population will be determined programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock and selection of the clinically relevant ones may be performed if needed.

All-important protocol deviations leading to exclusion from the PP population occurring during the study will be reviewed and approved by Pharma Mar prior to database lock. Should additional important protocol deviations leading to exclusion from the PP population, not anticipated at the time of preparing this SAP, be identified during the study they will be documented in separate document and included in all relevant protocol deviation reviews and approvals.

# 6. Data Handling

## 6.1 Time points and Visit Windows

Day 1, defined as the day of the first study drug administration.

Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1; there is no Day 0.

The following periods defined in Table 1.1 will be used for the analyses of the secondary efficacy endpoints related to percentage of patients requiring high-flow oxygen, noninvasive mechanical ventilation, invasive mechanical ventilation or ECMO, ICU admission or patients receiving subsequent antiviral or immune-modulating drugs from Day 1 to Days 4, 8, 15, and 31.

**Table 1.1 Definition of periods**

| Period [a] | Acceptable period |
|---|---|
| From Day 1 to Day 4 | Days 1 to 4 (Day 1, Day 4) |
| From Day 1 to Day 8 | Days 1 to 8 (Day 1, Day 8) |
| From Day 1 to Day 15 | Days 1 to 15 (Day 1, Day 15) |
| From Day 1 to Day 31 | Days 1 to 31 (Day 1, Day 31) |

[a] relative to the date of the first study drug administration

The rest of the efficacy and safety analyses will use the nominal study scheduled visits as defined in the Study Schedule and eCRF.

## 6.2 Handling of Dropouts, Missing Data, Intercurrent Events and Outliers

Patients with no available data for any time-to event efficacy endpoint will be censored at time 0.

For TFLs where calculation needs the first drug administration date, e.g. time between onset date of COVID-19 symptoms and initiation of study treatment (days), in patients randomized but not treated the randomization date will be used.

In the ISARIC-4 programming calculation a Glasgow coma scale score of 15 is assumed for all the patients.

Missing data, except dates, will not be imputed for safety analyses. The safety evaluations will be performed on observed data only.

For AEs with partial or missing onset or stop dates:

- AE stop date will be imputed first as:
  - If stop date is completely missing, assume it is ongoing (no imputation);
  - For a partial AE stop date:
    - day is missing, then take the last day of the month
    - both day and month are missing, then take December 31st.
  - If the imputed AE stop date is after the End of the Study date, then the stop date will be set to the End of the Study date.
- Then AE onset date will be imputed as:
  - If onset date is completely missing: the first dose date;
  - For a partial AE onset date
    - day is missing:

- Partial date < the first dose date: last day of the month
- Partial date = the first dose date: the first dose date
- Partial date > the first dose date: first day of the month

▪ both day and month are missing, ie, only the year is available:

- Partial date < the first dose date: December 31st
- Partial date = the first dose date: the first dose date
- Partial date > the first dose date: January 1st

o If the imputed AE onset date is after the AE stop date/imputed AE stop date, then the onset date will be set to the AE stop date/imputed AE stop date.

The imputed dates will not be listed. Study day relative to the first dose of study drug associated with missing or partial dates will not be displayed in AE listings.

In the event that a partial date (month/year or year) for concomitant medication is available, concomitant medication start and stop dates will be imputed as:

- When both month and year are available – first day of the month will be used for start date and the last day of the month will be used for the stop date.
- When only year is available – January 1st will be used for the start date and December 31st will be used for the stop date.

The imputed dates will only be used to determine whether a concomitant medication will be classified as prior medication or concomitant medication.

For intercurrent events, the number and percentage of patients who complete the study including a breakdown of the primary reasons for treatment discontinuation will be shown. Percentage and potential impact of patients receiving subsequent antiviral therapies or immunomodulatory drugs after treatment start and subgroup analyses will be also presented. Finally, different population subsets and supportive/sensitivity analyses for the main endpoints will be also presented.

No rules for outlier detection are planned.

# 7. Statistical Methods

## 7.1 General Principles

All data processing, summarization and analyses will be performed using Labcorp Drug Development's SAS® Environment / Version 9.4 (or later) of the SAS® statistical software package.

The following principles will be applied to all tables, figures and listings (TFLs) unless otherwise stated:

| Principle | Value |
|---|---|
| Significant tests | All significance tests will be 2-sided and use a 0.05 α-level unless specified otherwise, eg primary and key secondary efficacy endpoint analysis explained below. |
| Treatment group labels and order presented | Plitidepsin 2.5mg<br>Plitidepsin 1.5mg<br>Control Arm |
| Tables | Data in summary tables presented by treatment group, assessment/parameter (where applicable) and visit (where applicable). |
| Listings | All data collected presented by treatment group, country, site, patient, assessment/parameter (where applicable) and visit (where applicable), unless otherwise specified. |
| Descriptive summary statistics for continuous variables | Number of patients/observations with non-missing data (n), mean, standard deviation (SD), median, interquartile range ($25^{th}$ and $75^{th}$ percentiles), range (minimum and maximum). If n=0 then other statistics will be blank. |
| Descriptive summary statistics for categorical variables | Frequency counts and associated percentages [n (%)] or difference in percentages presented to 1 decimal place. |
| Denominator for percentages | Number of patients per treatment group in the analysis population, unless stated otherwise in table shell(s). |
| Include "Missing" as category | Yes, when the number missing is greater than zero for at least one treatment group. |
| Display for 0 percentages | Leave <Blank> |
| Display to one more decimal place than collected value | Mean<br>Mean Difference<br>Median<br>$25^{th}$ and $75^{th}$ percentiles<br>Confidence Interval (CI) |
| Display to two more decimal places than collected value | SD<br>Standard Error (SE) |
| Display for p-values | x.xxxx for p-value ≥ 0.0001<br>< 0.0001 for p-value < 0.0001 |
| Display for hazard and odds ratio and the corresponding 95% CI | 3 decimal places |
| Date Format | DDMMMYYYY |
| Display for analysis not done | NC (not calculated), NA (not applicable), ND (not done), or NR (not reached). Refer to table shells. |

## 7.2 Patient Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by treatment group and overall and will include the number and percentage of patients:

- screened;
- randomised;

- randomised and treated;
- randomised and not treated;
- included in each study population (ITT, As Treated population, FAS, and PP).

The number and percentage of patients who complete the study and who discontinue early, including a breakdown of the primary reasons for study discontinuation, will be presented for the ITT population. In addition, the number of patients who complete the study treatment and who discontinue early, including a breakdown of the primary reasons for study treatment discontinuation, will be presented for the As Treated population.

A summary of patients randomised by country and site will also be provided by treatment group and overall for the ITT population.

A summary of the reasons for screen failure as well as the number of patients screened but not randomised will be produced. No other information for screen failures will be presented.

A summary of the randomisation stratification factors will also be provided by treatment group and overall for the ITT population, strata will be summarised as below:

- Geographical Region (Europe, Rest of the World) (as it was auto populated in the IRT system based on the country of the sites);
- Charlson comorbidity index (0-1, 2 or Greater) (as collected in the interactive response technology [IRT] system);
- Charlson comorbidity index (0-1, >1) (as derived using the Charlson comorbidity index data collected in the eCRF);
- Pre-baseline Barthel index (≥90 versus <90) (as collected in the interactive response technology [IRT] system);
- Pre-baseline Barthel index (≥90 versus <90) (as derived using the pre-baseline Barthel index data collected in the eCRF)

## 7.3 Protocol Deviations

All-important protocol deviations leading to exclusion from the PP population (see Section 5.4.1) will be summarized by treatment group and overall for the ITT population. All-important protocol deviations will be listed for the randomised population.

## 7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for the ITT population. Standard descriptive statistics will be presented for the continuous variables of:

- age (years);
- weight (kg) at Screening, to convert pounds to kilograms, multiply the pound value by 0.45359237;
- height (cm) at Screening, to convert inches to centimeters, multiply the inches value by 2.54;
- body mass index ($kg/m^2$) at Screening (calculated as [$weight/height^2$] where weight is in kg and height is in m);
- body surface area ($m^2$) at Screening (calculated using the Dubois and Dubois formulae as [$weight^{0.425} \times height^{0.725} \times 0.007184$] where weight is in kg and height is in cm)
- systolic blood pressure (mmHg) at Screening;
- diastolic blood pressure (mmHg) at Screening;
- pulse rate (beats/min) at Screening;
- temperature (C) at Screening, to convert Fahrenheit (F) to Celsius, (Fahrenheit value (F) – 32) * 5/9;
- respiration rate (breaths/min) at Screening;
- oxygen saturation at room air (%) at Screening

The total counts and percentages of patients will be presented for the categorical variables of:

- age group (years) (grouped as [18 to 39], [40 to 64], ≥ 65 years);
- sex;
- child bearing potential (females only; classified as [yes], [no, surgically sterile/post menopausal], [no, other]);
- race;
- ethnicity;
- body mass index group (grouped as < 18.5, ≥ 18.5 and < 25, ≥ 25 and < 30, ≥ 30 and < 35, ≥ 35 and < 40, ≥ 40);
- chest imaging at enrolment (pulmonary infiltrates, pleural fluid, atelectasis, pulmonary oedema, bilateral pneumonia, lateral pneumonia, other)

Other Baseline measurements, such as functional status, laboratory evaluations, and ECG will be summarized by treatment group with the post-Baseline measurements.

No formal tests of statistical significance will be performed on the demographic and Baseline data.

### 7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 24 [or a later version if updated during the study]). All medical history will be listed, and the number and percentage of patients with any active or past medical history will be summarized for the ITT population by system organ class (SOC) and grouped preferred term (PT) for each treatment group and overall for the ITT population. Separate summaries will be presented for active and past medical history, where active is defined as ticked on eCRF as ongoing (with or without treatment) and otherwise, is defined as past.

The final list of SOCs and PTs that are grouped after physician's review will be described in the 'Analysis Set Specification' document to ensure the latest MedDRA version is used for the analyses.

### 7.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with study drug will be coded using the World Health Organization (WHO) Drug Dictionary (Version 2021 [or a later version if updated during the study]), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken prior to the first dose date of any study drug administration, and with a stop date before first dose date of any study drug administration.
- Concomitant medications are those with a start date on or after the first dose date of any study drug administration, or those with a start date before the first dose date of any study drug administration and a stop date on or after the first dose date of any study drug administration or ongoing end of study.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications, concomitant medications (excluding COVID-19 antiviral therapies or immunomodulatory concomitant medications), and COVID-19 antiviral therapies or immunomodulatory concomitant medications will be summarized separately by treatment group and overall for the ITT population.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic subgroup (ATC-Level 2), chemical subgroup (ATC-Level 4), and grouped preferred term.

The final list of ATCs and PTs that are grouped after physician's review will be described in the 'Analysis Set Specification' document to ensure the latest WHO-ATC version is used for the analyses.

Prior medications, concomitant medications and COVID-19 antiviral therapies or immunomodulatory concomitant medications will be listed separately.

### 7.4.3 Signs and Symptoms

Time between onset date of COVID-19 symptoms and initiation of study treatment will be defined as:

Time between onset date of COVID-19 symptoms and initiation of study treatment (days) = (date of the first study drug administration – onset date of COVID-19 symptoms)

In patients randomized but not treated the randomization date will be used instead of the first study drug administration date.

Standard descriptive statistics will be presented for the time between the onset date of COVID-19 symptoms and initiation of study treatment by treatment group and overall for the ITT population.

The number and percentages of patients will be presented for the following signs and symptoms: history of fever, cough, sore throat, runny nose (rhinorrhoea), wheezing, shortness of breath, lower chest wall indrawing, chest pain, conjunctivitis, lymphadenopathy, headache, loss of smell (anosmia), loss of taste (ageusia), seizures, fatigue/malaise, anorexia, altered consciousness/confusion, muscle aches (myalgia), joint pain (arthralgia), inability to walk, abdominal pain, diarrhoea, vomiting/nausea, skin rash, bleeding (haemorrhage), and other symptom(s).

Signs and symptoms will be listed and summarized by treatment group and overall for the ITT population.

## 7.5 Measurements of Treatment Compliance

Not applicable.

## 7.6 Efficacy

Analysis of the primary, key secondary and other time-to-event efficacy endpoints will be performed in the ITT population. Other secondary efficacy endpoints will be based on the FAS population. A sensitivity analysis will be performed for the primary endpoint, key secondary and other time-to-event efficacy endpoints in the FAS population. Supportive analyses of the primary and key secondary efficacy endpoint will be performed on the PP population.

In all analyses (ITT, FAS and PP), the correct value of the stratification strata as derived using the Charlson comorbidity index and the pre-baseline Barthel index

data collected in the eCRF will be used instead of the investigator-derived value from IRT.

### 7.6.1 Primary Efficacy Analysis

Time to sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

Patients who reported sustained withdrawal of oxygen supplementation will be considered as an event on the date when patient meets categories 0 to 4 on the 11-point WHO Clinical Progression Scale and has no subsequent reutilisation of oxygen supplementation. Otherwise, in case of early study discontinuation due to any reason the patient will be censored at the date of the early study discontinuation. Otherwise, the patient will be censored at the date of the Day 31 visit or death date, whichever is first. If the patient was lost to follow-up between day 15 and day 31 visit, and there is an attempt of contact and study discontinuation on or after the day 31 visit due date, the patient will be censored at day 31.

Time-to sustained withdrawal of oxygen supplementation (days) =
(date of event or censoring – date of randomisation)

If date of event is the same as the randomisation date then time-to sustained withdrawal of oxygen supplementation will be considered as 1 day. If no data is available then time will be censored at time 0.

Time-to sustained withdrawal of oxygen supplementation will be analysed using the Kaplan-Meier method and 25$^{th}$ percentile, median and 75$^{th}$ percentile time will be presented by treatment group together with 95% CIs. The 95% CIs will be computed based on Brookmeyer-Crowley method and using a log log transformation. The mean time to sustained withdrawal of oxygen supplementation and its standard error will be also presented by treatment group.

Time-to sustained withdrawal of oxygen supplementation between each dose of plitidepsin versus control arm will be compared using a stratified log-rank test, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data. The 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

The 2-sided p-values from the stratified log-rank test will be adjusted for multiplicity using the Hochberg step-up procedure to preserve the type 1 error rate in the comparison of each dose of plitidepsin versus control arm. The Hochberg step-up procedure will be implemented as following:

- Let $p_1 \leq p_2$ denote the ordered unadjusted 2-sided p-values with associated null hypotheses $H_{01}$ and $H_{02}$, where $H_{0i}$ = time to sustained withdrawal of oxygen supplementation in plitidepsin [1.5 mg or 2.5 mg] arm = time to sustained withdrawal of oxygen supplementation in control arm.
- Then we follow the next stepwise procedure:
  - If $p_2 \leq 0.05$, reject $H_{01}$ and $H_{02}$ stop; else continue
  - If $p_1 \leq 0.05/2$, reject $H_{01}$ and stop
- Adjusted 2-sided p-values will be calculated as:
  - $q_2 = p_2$
  - $q_1$ = min[2*$p_1$,$q_2$]

The adjusted 2-sided p-values for multiplicity using the Hochberg step-up procedure will be also presented.

As supportive analyses:

- A stratified Cox proportional-hazards regression model, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data, will be applied to compare results between each dose of plitidepsin versus control arm. Hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.
- A Bootstrap analysis simulating the original sample size (n=203 per treatment group) will be implemented with the actual sample size in order to investigate what would have been the variability of the observed hazard ratio and the confidence interval if the trial's recruitment would not be stopped. Bootstrap resamples simulating the original sample size (n=203 per treatment group, n=609 in total and 10000 replications) will be created and a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group will be applied to compare results between each dose of plitidepsin versus control arm. The median value of the hazard ratios, the corresponding 95% CIs calculated as the 2.5% and 97.5% percentiles of the hazard ratios, and the median of the 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented. In addition, the percentage of samples with Hazard Ratio > 1 and the percentage of samples with 2-sided p-value < 0.025 will be also shown.

- The inconsistencies between the 11-point WHO Clinical Progression Scale and the oxygen supplementation status will be incorporated in an extended definition of the primary efficacy endpoint, i.e., time to sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient
    i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale ***or 'No supplemental oxygen needed' is recorded in the 'Vital Sign Oxygen status' form***, and
    ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale ***or any oxygen supplementation is recorded in the 'Vital Sign Oxygen status' form***)

The cumulative proportion of sustained withdrawal of oxygen supplementation (1-cumulative survival) will be displayed graphically by treatment group using a Kaplan-Meier curve.

The primary efficacy analysis described above will be performed using the ITT population. A sensitivity analysis using the same model will be performed in the FAS population and a supportive analysis using the same model will be performed using the PP population.

If the accrual in any of the experimental arm is stopped after the interim analysis, the final analysis for the primary endpoint in the remaining arms will be performed at the 1.25% (1-sided) or 2.5% (2-sided) level using a Bonferroni-adjusted type I error rate.

### 7.6.2 Secondary Efficacy Analysis

Analysis of the key secondary and other time-to-event efficacy endpoints will be based on the ITT population. Other secondary efficacy endpoints will be based on the FAS population. A sensitivity analysis will be performed for the primary key secondary and other time-to-event efficacy endpoints in the FAS population. Descriptive statistics for all the secondary efficacy endpoints will be presented by treatment group and by study visit where appropriate. Data from all study visits, scheduled and unscheduled will be listed.

#### 7.6.2.1 Key Secondary Efficacy Endpoint

Time to sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient

i. discharges from the hospital, and
ii. has no subsequent re-admission

Patients who reported sustained hospital discharge will be considered as an event on the date of discharge. Otherwise, in case of early study discontinuation due to any reason the patient will be censored at the date of the early study discontinuation. Otherwise, the patient will be censored at the date of the Day 31 visit or death date, whichever is first.

Time-to sustained hospital discharge (days) = (date of event or censoring – date of randomisation)

If date of event is the same as the randomisation date then time-to sustained hospital discharge will be considered as 1 day. If no data is available then time will be censored at time 0.

Time-to sustained hospital discharge will be analysed using the Kaplan-Meier method and 25$^{th}$ percentile, median and 75$^{th}$ percentile time will be presented by treatment group together with 95% CIs. The 95% CIs will be computed based on Brookmeyer-Crowley method and using a log log transformation. The mean time to hospital discharge and its standard error will be also presented by treatment group.

Time-to sustained hospital discharge between each dose of plitidepsin versus control arm will be compared using a stratified log-rank test, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data. The 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

In the event that the primary efficacy endpoint of time to sustained withdrawal of oxygen supplementation is significant for both doses in the ITT population, the 2-sided p-values from the stratified log-rank test for the key secondary efficacy endpoint will be adjusted for multiplicity using the Hochberg step-up procedure to preserve the type 1 error rate in the comparison of each dose of plitidepsin versus control arm. This adjustment will not apply if the accrual in any of the experimental arms is stopped after the interim analysis.

For the key secondary efficacy endpoint, the Hochberg step-up procedure will be used to test the key secondary efficacy endpoint at the overall (2-sided) significance level as following:

- Let $p_1 \leq p_2$ denote the ordered unadjusted 2-sided p-values with associated null hypotheses $H_{01}$ and $H_{02}$, where $H_{0i}$ = time to sustained hospital discharge in plitidepsin [1.5 mg or 2.5 mg] arm = time to sustained hospital discharge in control arm.
- Then we follow the next stepwise procedure:
    - If $p_2 \leq 0.05$, reject $H_{01}$ and $H_{02}$ stop; else continue

- If $p_1 \leq 0.05/2$, reject $H_{01}$ and stop
- Adjusted 2-sided p-values will be calculated as:
  - $q_2 = p_2$
  - $q_1 = \min[2*p_1, q_2]$

The adjusted 2-sided p-values for multiplicity using the Hochberg step-up procedure will be also presented.

As a supportive analyses, a stratified Cox proportional-hazards regression model, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), and Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data, will be applied to compare results between each dose of plitidepsin versus control arm. Hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

The cumulative proportion of sustained hospital discharge (1-cumulative survival) will be displayed graphically by treatment group using a Kaplan-Meier curve. The key secondary efficacy analysis described above will be performed using the ITT population. A sensitivity analysis using the same model will be performed in the FAS population and a supportive analysis using the same models will be performed using the PP population.

#### 7.6.2.2 Secondary Efficacy Endpoints

Descriptive statistics for the secondary efficacy endpoints will be presented by treatment group and by study visit where appropriate.

- *Clinical status by the 11 category WHO Clinical Progression Scale, at Day 8 (±1).*

  The clinical status, as assessed on the 11-point WHO Clinical Progression Scale on Day 8 will be summarised by treatment group. The percentage of patients within each category will be presented and the 95% CI will be computed using the Goodman method for the multinomial proportions.

  In case of missing clinical status on Day 8, the following approach will be used:

  - If patient dies before or on Day 8 → clinical status = 10.
  - Otherwise, the last observation carried forward (LOCF) approach will be used, where the last recorded clinical status for the same patient is carried forward to the missing clinical status on Day 8.

  The clinical status on Day 8 between each dose of plitidepsin versus control arm will be compared using a proportional odds model. The model will be adjusted for the randomisation stratification factors. The odds ratios, 95%

CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

- *Total duration of advanced oxygen support (high-flow nasal oxygen, ECMO, non-invasive ventilation or mechanical ventilation).*

  The total duration of advanced oxygen support (in days), defined as the number of days with any type of advanced oxygen support (eg, high-flow nasal oxygen, non-invasive mechanical ventilation, invasive mechanical ventilation or ECMO)

  Duration of advanced oxygen support (days) = (date of last advanced oxygen support required – date of randomisation) + 1 – off-advanced oxygen support days

  If last advanced oxygen support date is missing then date of death or the last visit or the last telephone contact with the patient, whichever occurs later, will be used.

  The number and percentage of patients who required an advanced oxygen support together with total duration of advanced oxygen support (in days) will be summarised by treatment group. Only patients who required an advanced oxygen support will be included in the summary of the total duration of advanced oxygen support.

- *Percentage of patients in each study group requiring admission to ICU on Days 4, 8, 15, and 31.*

  The percentage of patients who require admission to ICU at some time from Day 1 to Day 4, from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 31 will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

  The difference in the percentage of patients who require admission to ICU at some time during each period between each dose of plitidepsin versus control arm will be presented for each dose of plitidepsin and the exact 95% CI will be computed for the difference in the percentage.

  The percentage of patients who require admission to ICU at some time from Day 1 to Day 8 between each dose of plitidepsin versus control arm will be compared using a stratified logistic regression model. The model will be adjusted for the randomisation stratification factors. The odds ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

### 7.6.2.3 Other Secondary Efficacy Endpoints

Descriptive statistics for the other secondary efficacy endpoints will be presented by treatment group and by study visit where appropriate.

For time-to-event endpoints, similar methods will be used as specified for the analyses of the primary variable. For binary endpoints, the treatment group comparisons will be performed at Day 8 only, with descriptive statistics provided for each clinic visit.

- *Percentage of patients in each study group who require hospital re-admission related to COVID-19 through Day 31.*

  The percentage of patients who require re-admission for COVID-19 related signs or symptoms through Day 31 will be presented by treatment group and Clopper–Pearson 95% CI will be computed for the binomial proportion.

  Only patients who discharged from the hospital will be included in the analysis of the re-admission for COVID-19 related signs or symptoms.

- *Percentage of patients in each study group and in each of the categories of the 11-point WHO Clinical Progression Scale on Days 4, 8, 15, and 31.*

  The clinical status, as assessed on the 11-point WHO Clinical Progression Scale will be summarised on Days 4, 8, 15, and 31, by treatment group.

  In case of missing clinical status at the time point, the following approach will be used:

  - If patient dies before or on the time point → clinical status = 10.
  - Otherwise, LOCF approach will be used, where the last recorded clinical status for the same patient is carried forward to the missing clinical status at the time point.

- *Percentage of patients in each study group requiring oxygen therapy on Days 4, 8, 15, and 31.*

  The percentage of patients who require oxygen therapy on Days 4, 8, 15, and 31, will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

  If a patient requires any change in the oxygen therapy on Day 4, 8, 15, or 31, the new oxygen status will be selected, e.g. if a patient changes from ”Low-flow” to “No supplemental oxygen needed” on Day 4, “Require oxygen therapy on Day 4” = No. On the other hand, if a patient changes from ”No supplemental oxygen needed” to ”Low-flow” on Day 8, “Require oxygen therapy on Day 8” = Yes.

  The difference in the percentage of patients who require oxygen therapy on Days 4, 8, 15, and 31 between each dose of plitidepsin versus control arm

will be presented for each dose of plitidepsin and the exact 95% CI will be computed for the difference in the percentage.

The oxygen therapy rate on Day 8 between each dose of plitidepsin versus control arm will be compared using a stratified logistic regression model. The model will be adjusted for the randomisation stratification factors. The odds ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

Moreover, the percentage of patients who require oxygen therapy at some time from Day 1 to Day 4, from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 31, will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

The difference in the percentage of patients who require oxygen therapy at some time during each period between each dose of plitidepsin versus control arm will be presented for each dose of plitidepsin and the exact 95% CI will be computed for the difference in the percentage.

The percentage of patients who require oxygen therapy at some time from Day 1 to Day 8 between each dose of plitidepsin versus control arm will be compared using a stratified logistic regression model. The model will be adjusted for the randomisation stratification factors. The odds ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

- *Time to intensification of respiratory support (WHO >6 [intubation]).*

  Time to intensification of respiratory support (in days), defined as the first day, from randomisation through completion of the study, on which a patient satisfies a category > 6 on the 11-point WHO Clinical Progression Scale.

  Patients who reported a category > 6 on the 11-point WHO Clinical Progression Scale or died due to any cause through the study will be considered as an event on the first day on which a patient satisfies a category > 6 on the 11-point WHO Clinical Progression Scale or date of death, whichever occurs first. Otherwise, patients will be censored at the date of the last visit or telephone contact with the patient.

  Time-to intensification of respiratory support (days) = (date of event or censoring – date of randomisation)

  If date of event is the same as the randomisation date then time-to intensification of respiratory support will be considered as 1 day. If no data is available then time will be censored at time 0.

Time-to intensification of respiratory support will be analysed using the Kaplan-Meier method and 25$^{th}$ percentile, median and 75$^{th}$ percentile time will be presented by treatment group together with 95% CIs. The 95% CIs will be computed based on Brookmeyer-Crowley method and using a log log transformation. The mean time to intensification of respiratory support and its standard error will be also presented by treatment group.

Time-to intensification of respiratory support between each dose of plitidepsin versus control arm will be compared using a stratified log-rank test, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data. The 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

A stratified Cox proportional-hazards regression model, including the randomisation stratification factors as covariates, will be applied to compare results between each dose of plitidepsin versus control arm. Hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented. The cumulative survival will be displayed graphically by treatment group using a Kaplan-Meier curve.

- *Total duration of ICU stay for each study group.*

  The total duration of ICU stay (in days), defined as the number of days in ICU

  Duration of ICU stay (days) = (last date in ICU – date of admission in ICU) + 1 – off-ICU days

  The number and percentage of patients who were admitted in ICU together with the total duration of ICU stay (in days) will be summarised by treatment group.

  Only patients who were admitted in ICU will be included in the analysis of the duration of ICU stay.

- *Percentage of patients in each study group requiring high-flow oxygen on Days 4, 8, 15, and 31.*

  The percentage of patients who require high-flow oxygen on Days 4, 8, 15, and 31, will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

  Similarly, this endpoint will be analyzed as oxygen therapy rate.

- *Percentage of patients in each study group requiring non-invasive mechanical ventilation on Days 4, 8, 15, and 31.*

The percentage of patients who require non-invasive mechanical ventilation on Days 4, 8, 15, and 31, will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

Similarly, this endpoint will be analyzed as oxygen therapy rate.

- *Percentage of patients in each study group requiring invasive mechanical ventilation or ECMO on Days 4, 8, 15, and 31.*

  The percentage of patients who require invasive mechanical ventilation or ECMO on Days 4, 8, 15, and 31, will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

  Similarly, this endpoint will be analyzed as oxygen therapy rate.

- *Time to initiation with immune-modulating drugs.*

  Time to initiation with immune-modulating drugs, defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent immune-modulating drugs.

  Patients who started subsequent immune-modulating drugs will be considered as an event on the first date of starting a subsequent immune-modulating drug. Otherwise, in case of early study discontinuation due to any reason the patient will be censored at the date of the early study discontinuation. Otherwise, the patient will be censored at the date of the Day 31 visit or death date, whichever is first.

  Time-to initiation with immune-modulating drugs (days) = (date of event or censoring – date of randomisation)

  If date of event is the same as the randomisation date then time-to initiation with immune-modulating drugs will be considered as 1 day. If no data is available then time will be censored at time 0.

  Time-to initiation with immune-modulating drugs will be analysed using the Kaplan-Meier method and $25^{th}$ percentile, median and $75^{th}$ percentile time will be presented by treatment group together with 95% CIs. The 95% CIs will be computed based on Brookmeyer-Crowley method and using a log log transformation. The mean time to initiation with immune-modulating drugs and its standard error will be also presented by treatment group.

  Time-to initiation with immune-modulating drugs between each dose of plitidepsin versus control arm will be compared using a stratified log-rank test, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), and Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus

<90) as derived using the eCRF data. The 2 sided p values for the comparison of each dose of plitidepsin versus control arm will be presented.

A stratified Cox proportional-hazards regression model, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), and Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data, will be applied to compare results between each dose of plitidepsin versus control arm. Hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

The cumulative survival will be displayed graphically by treatment group using a Kaplan-Meier curve.

- *Time to initiation with antiviral drugs.*

  Time to initiation with antiviral drugs, defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent antiviral drugs.

  Patients who started subsequent antiviral drugs will be considered as an event on the first date of starting a subsequent antiviral drug. Otherwise, in case of early study discontinuation due to any reason the patient will be censored at the date of the early study discontinuation. Otherwise, the patient will be censored at the date of the Day 31 visit or death date, whichever is first.

  Time-to initiation with antiviral drugs (days) = (date of event or censoring – date of randomisation)

  If date of event is the same as the randomisation date then time-to initiation with immune-modulating drugs will be considered as 1 day. If no data is available then time will be censored at time 0.

  Similarly, this endpoint will be analyzed as time to initiation with immune-modulating drugs.

- *Percentage of patients receiving subsequent immune-modulating drugs on Days 4, 8, 15, and 31.*

  The percentage of patients receiving immune-modulating drugs at some time from Day 1 to Day 4, from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 31 will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

  Similarly, this endpoint will be analyzed as ICU admission rate.

- *Percentage of patients receiving subsequent antiviral drugs on Days 4, 8, 15, and 31.*

The percentage of patients receiving antiviral drugs at some time from Day 1 to Day 4, from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 31 will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

Similarly, this endpoint will be analyzed as ICU admission rate.

- *Percentage of patients in each study group with nosocomial infection by Days 4, 8, 15 and 31.*

  The 'Nosocomial infections' will be determined using the AE lowest level terms (LLT) and PTs. The LLTs that determine the 'Nosocomial infections' are 'Nosocomial infection' (PT: Nosocomial infection) and 'Nosocomial pneumonia' (PT: Pneumonia), based on MedDRA version 24.0. The final list of PTs that determine the 'Nosocomial infections' will be described in the 'Analysis Set Specification' document to ensure the latest MedDRA version is used for the analyses. As a supportive analysis a wider definition will also be considered, AEs with SOC term 'Infections and infestations' will be discussed with Labcorp Medical Monitor and will be defined according to Centers for Disease Control and Prevention's health care associated infection definition. [1] The final list of AEs or PTs that determine the wider definition of 'Nosocomial infections' will be described in the 'Analysis Set Specification' document to ensure the latest MedDRA version is used for the analyses.

  The percentage of patients with nosocomial infection at some time from Day 1 to Day 4, from Day 1 to Day 8, from Day 1 to Day 15, and from Day 1 to Day 31 will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

- Similarly, this endpoint will be analyzed as ICU admission rate.*Mortality in each study group on Days 4, 8, 15, and 31.*

  Overall survival defined as the time from randomisation to death due to any cause. Patients who died through the study due to any cause will be considered as an event on the date of death. Otherwise, patients who were alive or lost to follow-up at the end of the study will be censored at the date at which the patient was last known to be alive.

  Overall survival (days) = (date of death or censoring – date of randomisation)

  The date at which the patient was last known to be alive will be the latest date obtained from: visit/assessment dates (with valid assessment measures, ie, non-blank), AE start and stop dates (except AEs with fatal outcome), concomitant medications start and stop dates and concomitant procedure dates.

**Note**: For the interim analysis, overall survival is defined as the elapsed time to death if a patient died on or prior to the cutoff date. If a patient's live/death status is known between cutoff date and the actual interim analysis extract date, then the patient is censored on the cutoff date. Otherwise, if a patient is only known to be alive prior to the cutoff date, then the patient is censored at the last known alive date.

Overall survival will be analysed using the Kaplan-Meier method and 25$^{th}$ percentile, median and 75$^{th}$ percentile time will be presented by treatment group together with 95% CIs. The 95% CIs will be computed based on Brookmeyer-Crowley method and using a log log transformation. The mean survival time and its standard error will be also presented by treatment group. Additionally, mortality rates by Days 4, 8, 15, and 31 will be presented together with 95% confidence bands. The 95% confidence bands will be computed based on Hall-Wellner method.

Overall survival between each dose of plitidepsin versus control arm will be compared using a stratified log-rank test, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data. The 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

A stratified Cox proportional-hazards regression model, including the randomisation stratification factors as covariates, will be applied to compare results between each dose of plitidepsin versus control arm. Hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented. The cumulative proportion of mortality (1-cumulative survival) will be displayed graphically by treatment group using a Kaplan-Meier curve.

- *Change in the viral load of SARS-CoV-2 in each study group from Day 1 before administration of study drug until Day 8.*

  The change ($log_{10}$ copies/mL) from Day 1 visit to Day 8 visit will be calculated as the difference between Day 1 and Day 8 values, ie,

  change from Day 1 = Day 8 value – Day 1 value

  The viral load of SARS-CoV-2 ($log_{10}$ copies/mL) at Day 1 and Day 8, and the change from Day 1 in SARS-CoV-2 viral load at Day 8 will be summarized using standard descriptive statistics. Data from all study visits, scheduled and unscheduled, will be listed.

The change in viral load of SARS-CoV-2 at Day 8 between each dose of plitidepsin versus control arm will be compared using an analysis of covariance (ANCOVA) model fitted for the fixed effects of treatment group, the randomisation stratification factors, and the continuous fixed covariate of viral load of SARS-CoV-2 at Day 1.

The least squares (LS) means and SE for each treatment group, together with the LS mean differences, SE, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

Median viral load of SARS-CoV-2 together with the interquartile range will be plotted at Day 1 and Day 8.

**Note**: Prior to calculation of summary statistics: any individual values below the lower limit of quantification (<LLOQ) of the PCR technique will be replaced with LLOQ/2 for the calculation of summary statistics unless it is zero.

- *Percentage of patients in each study group with undetectable viral load of SARS-CoV-2 on Day 8.*

  The percentage of patients with undetectable viral load of SARS-CoV-2, ie, patients with viral load of SARS-CoV-2 < Limit of Detection (LOD), on Day 8 will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

  The difference in the percentage of patients with undetectable viral load of SARS-CoV-2 on Day 8 between each dose of plitidepsin versus control arm will be presented for each dose of plitidepsin and the exact 95% CI will be computed for the difference in the percentage.

  The undetectable viral load of SARS-CoV-2 on Day 8 rate between each dose of plitidepsin versus control arm will be compared using a stratified logistic regression model. The model will be adjusted for the randomisation stratification factors. The odds ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

  The percentage of patients with a reduction ≥ 2-log in viral load or undetectable viral load of SARS-CoV-2 on Day 8 will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

  The difference in the percentage of patients with a reduction ≥ 2-log in viral load or undetectable viral load of SARS-CoV-2 on Day 8 between each dose of plitidepsin versus control arm will be presented for each dose of plitidepsin and the exact 95% CI will be computed for the difference in the percentage.

The reduction ≥ 2-log in viral load or undetectable viral load of SARS-CoV-2 on Day 8 rate between each dose of plitidepsin versus control arm will be compared using a stratified logistic regression model. The model will be adjusted for the randomisation stratification factors. The odds ratios, 95% CIs, and 2 sided p values for the comparison of each dose of plitidepsin versus control arm will be presented.

- *Change in inflammatory biomarkers (CRP, ferritin, IL-1β, IL-6, IL-10, and TNFα) in each study group from baseline until Days 2, 3, 4, 8, and 31.*

  The Baseline value for the inflammatory biomarkers is defined as the value collected at the time of the clinic visit on Day 1. The percent change from Baseline at post-Baseline visits will be defined as:

  - For CRP, ferritin, referred to the upper limit of normal (ULN)

    % change from Baseline = 100*((post-Baseline value/ULN) – (Baseline value/ULN))/(Baseline Value/ULN)

    The values referred to ULN, ie, result/ULN, at baseline and at each post-Baseline visit, and the change from Baseline values will be summarized by Visit using standard descriptive statistics.
    The median values referred to ULN together with the interquartile ranges will be plotted over time by treatment group and visit.
    A spaghetti plot will also be used to represent the patient profile over time by treatment group.

  - For IL-1β, IL-6, IL-10, and TNFα

    % change from Baseline = 100*(post-Baseline value – Baseline value)/Baseline Value

    The values at baseline and at each post-Baseline visit, and the change from Baseline values will be summarized by Visit using standard descriptive statistics.
    The median values together with the interquartile ranges will be plotted over time by treatment group and visit.
    A spaghetti plot will also be used to represent the patient profile over time by treatment group.

  Data from all study visits, scheduled and unscheduled, will be listed.

- *Change respect to baseline in individual serological assessments.*

  The percentage of patients with a serologic response anti-SARS-CoV-2 at Day 31 will be presented by treatment group. Clopper–Pearson 95% CI will be computed for the binomial proportions.

The Baseline value for the serologic response anti-SARS-CoV-2 is defined as the immunoglobulin (Ig)G Antibodies quantification value collected at the time of the clinic visit on Day 1.

Patients are considered to have a serologic response anti-SARS-CoV-2 if:

- Baseline IgG Antibodies quantification is interpreted as negative (e.g. <0.8), borderline (e.g. ≥0.8 and <1.1) or missing and increases above the established boundary (e.g. ≥1.1), following study drug administration.
- Baseline IgG Antibodies are positive and the result at Day 31 sample is at least two-folds greater than the baseline sample.

All of the other options are considered as non-serologic response.

Cutoffs for IgG Antibodies quantification will be selected at the analysis time based on the latest available specifications of the selected technology.

The difference in the percentage of patients with a serologic response anti-SARS-CoV-2 between each dose of plitidepsin versus control arm will be presented for each dose of plitidepsin and the exact 95% CI will be computed for the difference in the percentage.

The percentage of patients with a serologic response anti-SARS-CoV-2 between each dose of plitidepsin versus control arm will be compared using a stratified logistic regression model. The model will be adjusted for the randomisation stratification factors. The odds ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

The IgG Antibodies quantification values at baseline and at Day 31 visit, and the change from Baseline in IgG Antibodies quantification values will be summarized using standard descriptive statistics.

The percent change in IgG Antibodies quantification from Baseline at Day 31 visit will be defined as:

$$\% \text{ change from Baseline} = 100*(\text{Day 31 value} - \text{Baseline value})/\text{Baseline Value}$$

Data from all study visits, scheduled and unscheduled, will be listed.

- *To compare efficacy in the primary endpoint and describe safety/tolerability of pooled plitidepsin arms versus control.*

  Time-to sustained withdrawal of oxygen supplementation will be analysed using the Kaplan-Meier method and 25$^{th}$ percentile, median and 75$^{th}$ percentile time will be presented for the pooled plitidepsin arms and control

arm, together with 95% CIs. The 95% CIs will be computed based on Brookmeyer-Crowley method and using a log log transformation. The mean time to sustained withdrawal of oxygen supplementation and its standard error will be also presented for the pooled plitidepsin arms and control arm.

Time-to sustained withdrawal of oxygen supplementation between of the pooled plitidepsin arms versus control arm will be compared using a stratified log-rank test, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data. The 2-sided p-values for the comparison of the pooled plitidepsin arms versus control arm will be presented.

A stratified Cox proportional-hazards regression model, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), and Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data, will be applied to compare results between the pooled plitidepsin arms and control arm. Hazard ratios, 95% CIs, and 2-sided p-values for the comparison of the pooled plitidepsin arms versus control arm will be presented.

The cumulative proportion of sustained withdrawal of oxygen supplementation (1-cumulative survival) will be displayed graphically for the pooled plitidepsin arms and control arm using a Kaplan-Meier curve.

- *To compare efficacy in the primary endpoint and describe safety/tolerability between plitidepsin arms (1.5 versus 2.5 mg) in case both arms are significantly superior to the control*.

  All summary tables will be presented by treatment group. Therefore, all the data needed to compare the efficacy and safety/tolerability between plitidepsin arms (1.5 versus 2.5 mg) will be already present in the outputs created for the other efficacy and safety endpoints. Statistical comparisons between Plitidepsin arms (1.5 versus 2.5 mg) will not be performed.

- *To explore the influence of risk factors or scores for clinical deterioration that were not individually included.*

  A subgroup analysis has been defined to assess this endpoint (see Section 7.6.4).

- *Time to sustained withdrawal of supplementary oxygen (11-category WHO Clinical Progression Scale ≤4) with no subsequent reutilisation during remaining study period, before (protocol v.6) and after the amendment (protocol v.7).*

A subgroup analysis has been defined to assess this endpoint (see Section 7.6.4).

- *Time to sustained (ie, with no subsequent readmission to Day 31) hospital discharge (since randomisation), before (protocol v.6) and after the amendment (protocol v.7)*

  A subgroup analysis has been defined to assess this endpoint (see Section 7.6.4).

### 7.6.3 Sensitivity Analysis

As a sensitivity analysis for the primary efficacy endpoint:

- For the Cox regression model of the primary efficacy endpoint, the proportional hazard assumption will be checked by means of a Cox regression including treatment and its time dependent covariate, i.e., treatment group*log(time). Censored patients at time 0 will not be used in the model.[2] In case of strong rejection of proportionality, ie, p-value < 0.05, then restricted mean survival estimates will be calculated at Days 4, 8, 15, and 31 and weighted log-rank tests (if applicable) will also be calculated in addition to the hazard ratios from the stratified Cox regression model.[3]
- Time-to sustained withdrawal of oxygen supplementation between each dose of plitidepsin versus control arm will be compared on the FAS population.
- Time-to sustained withdrawal of oxygen supplementation between each dose of plitidepsin versus control arm will be compared using an unstratified log-rank test and Cox regression model on the ITT population. The hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.
- If at least the 5% of the patients in any treatment group are mis-stratified then the time-to sustained withdrawal of oxygen supplementation between each dose of plitidepsin versus control arm will be compared using a stratified log-rank test and Cox regression model on the ITT population. The model will be adjusted for the randomisation stratification factors as they were collected in IRT, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. 2 or Greater) and Barthel index (≥90 versus <90) as collected in IRT. The hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

Moreover, as a sensitivity analysis for the key secondary efficacy endpoint:

- Time-to sustained hospital discharge between each dose of plitidepsin versus control arm will be compared on the FAS population.

- Time-to sustained hospital discharge between each dose of plitidepsin versus control arm will be compared using an unstratified log-rank test and Cox regression model on the ITT population. The hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

As a sensitivity analysis for the other time-to-event secondary efficacy endpoints, eg, time to initiation with immune-modulating or antiviral drugs, overall survival, and time to intensification of respiratory support:

- Each dose of plitidepsin versus control arm will be compared on the FAS population.
- Each dose of plitidepsin versus control arm will be compared using an unstratified log-rank test and Cox regression model on the ITT population. The hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

### 7.6.4 Subgroup Analysis

The primary and key secondary efficacy endpoint will be analysed using the ITT population by the following subgroups:

- Charlson Comorbidity index (as derived using the eCRF data): '0 – 1' or '> 1'
- Geographical Region: Europe or Rest of the World
- Pre-baseline Barthel index: '≥ 90' or '< 90'
- Patients included before and after amendment: 'Protocol v.6 or before' or 'Protocol v.7'

The same covariates used for the primary efficacy endpoint analysis will be used for the subgroup analyses except that for the Charlson Comorbidity index subgroup analysis, the randomisation stratum of Charlson Comorbidity index will not be included as a covariate; for the Geographical Region subgroup analysis, the randomisation stratum of Geographical Region will not be included as a covariate; and for the pre-baseline Barthel index subgroup analysis, the randomisation stratum of pre-baseline Barthel index will not be included as a covariate.

Additionally, the primary efficacy endpoint will be analysed by the following subgroups:

- Sex: female or male
- Age at study entry: '18 to 39', '40 to 64' or '≥ 65 years'
- Race: Asian, black, white or other
- Ethnic group: 'Hispanic or Latino' or 'Not Hispanic or Latino'

- Site location: each study site with more than 1/6 out of the randomised patients (ie, >33 randomised patients for the futility analysis and >101 randomised patients for the final analysis) will be considered as a group and the remaining study sites, ie, those study sites with less than 1/6 out of the randomised patients will be pooled together as a one single group.
- Use of antiviral therapies or immunomodulatory drugs through the study: Yes or No
- Previous COVID-19 vaccination status: 'Fully vaccinated', 'Non-fully vaccinated', 'No vaccinated', or 'Fully vaccinated + Non-fully vaccinated'
- Anti-SARS-CoV-2 IgG at Day 1: 'Non-positive' or 'Positive'
- Pre-randomisation dexamethasone: Yes or No
- Total duration of corticoid therapy: '< 9 days', '[9 – 11] days' or '> 11 days'
- Total cumulative dose of corticoid therapy (dexamethasone or equivalent): '≤ 60 mg' or '> 60 mg'
- SARS-CoV-2 viral load ($log_{10}$ copies/mL) at Day 1 before study drug administration: '< 4', '[4 - 7]' or '> 7'
- Time between onset date of COVID-19 symptoms and initiation of study treatment: '≤ 5 days', '6 - 10 days' or '> 10 days'
- Body mass index ($kg/m^2$) at Screening: < 30 or ≥ 30 (Obesity)
- Hypertension at Screening, defined as Hypertension (Standardised MedDRA Query [SMQ]) in the Medical History form: Yes or No
- Individual co-morbidities included in the Charlson Index: myocardial infarction (Yes or No), congestive heart failure (Yes or No), peripheral vascular disease (Yes or No), cerebrovascular disease (Yes or No), dementia (Yes or No), chronic obstructive pulmonary disease (Yes or No), connective tissue disease (Yes or No), peptic ulcer disease (Yes or No), liver disease ('None', 'Mild' or 'Moderate or Severe'), diabetes mellitus ('None or diet controlled', 'Uncomplicated' or 'End-organ damage'), hemiplegia (Yes or No), moderate or severe chronic kidney disease (Yes or No), solid tumor ('None', 'Localized' or 'Metastatic'), leukemia (Yes or No), lymphoma (Yes or No) or AIDS (Yes or No).
- ISARIC-4C mortality score: Low (0 - 3), Intermediate (4 - 8), High (9 - 14) or Very high (≥ 15)
- ISARIC-4C deterioration probability (%): '≤ 25', '(25 - 50]', or '> 50'
- Lactate dehydrogenase (LDH) at Baseline: ≤ ULN or > ULN

- CRP (mg/L) at Baseline: ≤ 100 or > 100
- D-dimer at Baseline: ≤ ULN or > ULN
- Ferritin at Baseline: ≤ ULN or > ULN
- Creatinine at Baseline: ≤ ULN or > ULN
- IL-6 at Baseline: ≤ Median or > Median value (at the analysis time cutoff may be updated based on distribution values if needed)
- IL-10 at Baseline: ≤ Median or > Median value (at the analysis time cutoff may be updated based on distribution values if needed)
- Lymphocytes count decreased at Baseline: 'Grade 0' or 'Grade ≥ 1'
- Neutrophils/lymphocytes ratio at Baseline: < 6 or ≥ 6
- SARS-CoV-2 variant: Alpha, Beta, Gamma, Delta, Eta, Iota, Kappa, Lambda, Mu, or any potential new variant

The same covariates used for the primary efficacy endpoint analysis will be used for the subgroup analyses.

For ISARIC-4C mortality score and deterioration probability calculation:

- A Glasgow coma scale score of 15 is assumed for all the patients.
- Urea (mmol/L) will be calculated as blood urea nitrogen (mmol/L) * 60 / 28.

Forest plots of the hazard ratios, and the 95% CI for the comparison of each dose of plitidepsin versus control arm will be presented by endpoint for all subgroups using the ITT population.

### 7.6.5 Exploratory Analysis

A multivariate analysis will be performed for the primary and key secondary efficacy endpoint, including the treatment group, randomisation stratification factors and all the above subgroup variables as covariates. Those covariates with more than 10% of missing values will be omitted from the multivariate analysis. A stepwise selection model will be used, with significant level equal to 0.2 and 0.05, to enter into the model and to remain in the model, respectively.Treatment group will be forced to be included in addition to the significant covariates.

Time-to sustained withdrawal of oxygen supplementation will be compared between each dose of plitidepsin versus control arm receiving the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir).

Time-to sustained withdrawal of oxygen supplementation will be analysed using the Kaplan-Meier method and 25$^{th}$ percentile, median and 75$^{th}$ percentile time will be presented for the plitidepsin arms and control arm receiving the antiviral control

arm, together with 95% CIs. The 95% CIs will be computed based on Brookmeyer-Crowley method and using a log log transformation. The mean time to sustained withdrawal of oxygen supplementation and its standard error will be also presented for the pooled plitidepsin arms and control arm.

Time-to sustained withdrawal of oxygen supplementation between each dose of plitidepsin versus control arm receiving the antiviral control arm will be compared using a stratified log-rank test, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data. The 2-sided p-values for the comparison of the pooled plitidepsin arms versus control arm will be presented.

A stratified Cox proportional-hazards regression model, including the randomisation stratification factors as covariates, ie, Geographical Region (Europe vs. Rest of the World), and Charlson Comorbidity index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data, will be applied to compare results between each dose of plitidepsin arms and control arm receiving the antiviral control arm. Hazard ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin arms versus control arm receiving the antiviral control arm will be presented.

Similarly, time-to sustained withdrawal of oxygen supplementation will be compared between each dose of plitidepsin versus control arm without receiving the antiviral control arm.

## 7.7 Safety

### 7.7.1 Extent of Exposure

Duration of exposure of each study drug, ie, plitidepsin, dexamethasone, and the regulatory-approved antiviral for those patients randomised to the control arm (ie, remdesivir or favipiravir), will be defined in days as:

(date of last dose of the relevant study drug taken – date of first dose of the relevant study drug taken) + 1.

If date of first dose date is missing then date of randomisation visit will be used.

Duration of exposure (as a continuous variable), total number of days with doses administered, the number of days where total amount was administered, the number of days where total amount was not administered and the number of infusions interrupted (as continuous and categorical variables only for plitidepsin, and the regulatory-approved antiviral for those patients randomised to the control arm, ie, remdesivir or favipiravir) will be listed and summarized using descriptive statistics for each treatment group and each study drug for the As Treated population.

### 7.7.2 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary (Version 24 [or a later version if updated during the study]) and classified as TEAEs as follows:

- TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it will not be considered as a TEAE.

All AE data will be listed by treatment group with TEAE status flagged in the listing. In addition, listings of grade ≥3 AEs, SAEs, AEs leading to discontinuation of any study drug, AEs resulting in death and AEs of special interest will be produced.

The AEs of special interest will be based on MedDRA version 24.0. The terms that determine the AEs of special interest are:

- For Rhabdomyolysis, Musculoskeletal disorders and CPK increases:
  - Rhabdomyolysis/Myopathy (SMQ)
  - Additional PTs: Back pain, Pain in extremity, Arthralgia
- For Hypersensitivity reactions:
  - Hypersensitivity (SMQ)
- For Cardiac events:
  - Cardiomyopathy (SMQ)
  - Cardiac arrhythmias (SMQ)
  - Cardiac failure (SMQ)
  - Additional PTs: Acute myocardial infarction, Cardiovascular insufficiency, Coronary artery disease, Myocardial infarction, Angina pectoris, Aortic valve incompetence, Aortic valve sclerosis, Atrial thrombosis, Cardiac disorder, Degenerative aortic valve disease, Left ventricular hypertrophy, Mitral valve incompetence, Myocardial ischaemia, Pericardial effusion, Pericarditis, Subendocardial ischaemia, Tricuspid valve incompetence, Blood creatine phosphokinase MB increased, Blood pressure increased, Cardiac murmur, Electrocardiogram QRS complex abnormal, Electrocardiogram ST segment abnormal, Electrocardiogram ST segment depression, Electrocardiogram ST-T change, Electrocardiogram ST-T segment abnormal, Electrocardiogram T wave abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram T wave inversion, Oxygen saturation decreased, Pulse abnormal, Respiratory rate,

Troponin increased, Troponin I increased, Troponin T increased, Acute respiratory failure, Apnoea, Dyspnoea exertional, Hyperventilation, Hypoventilation, Hypoxia, Tachypnoea, Diastolic hypertension, Hypovolaemic shock, Systolic hypertension.

- For Hepatobiliary disorders and Transaminase elevations:
  - Hepatobiliary disorders (SOC)
  - Liver function analyses (HLT)

The final list of terms that determine the AEs of special interest will be described in the 'Analysis Set Specification' document to ensure the latest MedDRA version is used for the analyses.

Summary tables of TEAEs by treatment group and overall plitidepsin will be produced for the As Treated population.

Assessment of AE severity will be based on the NCI-CTCAE, version 5.0.

A treatment-related TEAE to plitidepsin, dexamethasone or to the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir), is an TEAE considered by the investigator as related to the corresponding study drug or with unknown/missing relationship to trial medication.

An overview table will summarize the number and percentage of patients with at least one of the following TEAEs, where patients with more than one TEAE in a particular category are counted only once in that category:

- Any TEAE;
- Any TEAE by severity;
- Any TEAE grade ≥3;
- Any TEAE leading to discontinuation of any study drug;
- Any TEAE leading to death;
- Any treatment-related TEAE to any study drug;
- Any treatment-related TEAE grade ≥3 to any study drug;
- Any treatment-related TEAE to any study drug leading to discontinuation of any study drug;
- Any treatment-related TEAE to any study drug leading to death;
- Any treatment-related TEAE to plitidepsin;
- Any treatment-related TEAE grade ≥3 to plitidepsin;
- Any treatment-related TEAE to plitidepsin leading to discontinuation of any study drug;
- Any treatment-related TEAE to plitidepsin leading to death;

- Any treatment-related TEAE to dexamethasone;
- Any treatment-related TEAE grade ≥3 to dexamethasone;
- Any treatment-related TEAE to dexamethasone leading to discontinuation of any study drug;
- Any treatment-related TEAE to dexamethasone leading to death;
- Any treatment-related TEAE to antiviral control arm;
- Any treatment-related TEAE grade ≥3 to antiviral control arm;
- Any treatment-related TEAE to antiviral control arm leading to discontinuation of any study drug;
- Any treatment-related TEAE to antiviral control arm leading to death;
- Any serious TEAE;
- Any serious TEAE grade ≥3;
- Any serious TEAE leading to discontinuation of any study drug;
- Any serious TEAE leading to death;
- Any serious treatment-related TEAE to any study drug;
- Any serious treatment-related TEAE grade ≥3 to any study drug;
- Any serious treatment-related TEAE to plitidepsin;
- Any serious treatment-related TEAE to dexamethasone;
- Any serious treatment-related TEAE to antiviral control arm;
- Any TEAE of special interest;
- Any TEAE grade ≥3 of special interest;
- Any TEAE of special interest leading to discontinuation of any study drug;
- Any TEAE of special interest leading to death

The number and percentage of patients reporting each TEAE will be summarized by treatment group and overall plitidepsin, SOC and grouped PT for the As Treated population. Tables will be sorted alphabetically by SOC. Grouped PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs, by SOC and grouped PT;
- TEAEs by grouped PT;
- TEAEs by maximum severity, SOC and grouped PT;
- TEAEs leading to discontinuation of any study drug by SOC and grouped PT;
- TEAEs leading to death by SOC and grouped PT;

- Treatment-related TEAEs to any study drug (plitidepsin, dexamethasone or antiviral control arm) by SOC and grouped PT;
- Treatment-related TEAEs to any study drug (plitidepsin, dexamethasone or antiviral control arm) by maximum severity, SOC and grouped PT;
- Treatment-related TEAEs to plitidepsin by SOC and grouped PT;
- Treatment-related TEAEs to plitidepsin by maximum severity, SOC and grouped PT;
- Treatment-related TEAEs to dexamethasone by SOC and grouped PT;
- Treatment-related TEAEs to dexamethasone by maximum severity, SOC and grouped PT;
- Treatment-related TEAEs to antiviral control arm by SOC and grouped PT;
- Treatment-related TEAEs to antiviral control arm by maximum severity, SOC and grouped PT;
- Serious TEAEs by SOC and grouped PT;
- Serious TEAEs by maximum severity, SOC and grouped PT;
- Serious treatment-related TEAE to any study drug (plitidepsin, dexamethasone or antiviral control arm) by SOC and grouped PT;
- Serious treatment-related TEAE to any study drug (plitidepsin, dexamethasone or antiviral control arm) by maximum severity, SOC and grouped PT;
- Serious treatment-related TEAE to plitidepsin by SOC and grouped PT;
- Serious treatment-related TEAE to dexamethasone by SOC and grouped PT;
- Serious treatment-related TEAE to antiviral control arm by SOC and grouped PT.
- TEAEs of special interest by SOC and grouped PT;
- TEAEs of special interest by maximum severity, SOC and grouped PT.

In the above summaries, patients with more than one AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one AE within a particular grouped PT are counted only once for that grouped PT. For summaries by maximum severity, patients with multiple AEs within a particular SOC or grouped PT will be counted under the category of their most severe AE within that SOC or grouped PT.

The final list of SOCs and PTs that are grouped after physician's review will be described in the 'Analysis Set Specification' document to ensure the latest MedDRA version is used for the analyses.

In addition, summary tables of deaths and their causes (adverse event or other) by treatment group and overall plitidepsin will be produced for the As Treated population.

No formal statistical comparisons of AEs between treatment groups will be performed.

### 7.7.3 Laboratory Evaluations

Data for the haematology, serum chemistry, and coagulation analytes received from central laboratory will be listed and summarized by treatment group and overall plitidepsin, and visit. Haematology and serum chemistry analytes from local laboratories recorded at Screening in the eCRF will be listed only. If data for any additional analytes are also received then these will be listed only.

Immunology and Serological SARS CoV 2 data are summarised within the other secondary efficacy endpoints.

| **Haematology** | **Serum Chemistry** |
|---|---|
| Red Blood Cell Count<br>Haemoglobin<br>Haematocrit<br>White Blood Cell Count<br>Neutrophils<br>Eosinophils<br>Basophils<br>Lymphocytes<br>Monocytes<br>Platelet Count | Alanine aminotransferase (ALT)<br>Aspartate aminotransferase (AST)<br>Alkaline phosphatase<br>Gamma-Glutamyltransferase (GGT)<br>LDH<br>Total Bilirubin<br>Direct Bilirubin<br>Glucose (fasting)<br>Sodium<br>Potassium<br>Calcium (adjusted)<br>Magnesium<br>Blood Urea Nitrogen<br>Creatinine<br>Calculated Creatinine Clearance (Cockcroft-Gault equation)<br>Creatine Phosphokinase (CPK)<br>Albumin<br>Amylase<br>Lipase<br>Procalcitonin<br>Troponin T<br>N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) |
| **Immunology** | |
| CRP<br>Ferritin<br>IL-1β<br>IL-6<br>IL-10<br>TNFα | |
| **Other Samples** | |
| Pregnancy tests (females only) | |
| **Coagulation** | **Serological SARS CoV 2 testing** |
| D-dimer | IgG |

All central Laboratory data will be reported in International System of Units. Local Laboratory data will be listed in the Units that they were collected in the eCRF. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">" sign (ie, those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Central laboratory data will be summarized by visit using standard descriptive statistics by treatment group and overall plitidepsin for the As Treated population. Changes from Baseline will also be summarized. For post-Baseline, only data from scheduled visits will be included in the summary tables.

If more than 10% of the patients preform an unscheduled central laboratory assessment at the same relative day to the start date of study treatment then the central laboratory data will be also summarised at the specific relative day. In case of several unscheduled laboratory assessments at the same day we will use the worst result.

For each laboratory analyte, the Baseline value will be defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration. Central Laboratory assessments carried out on the day of first study drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded.

For haematology and serum chemistry analytes, laboratory abnormalities from central Laboratory analytes will be graded according to NCI-CTCAE version 5.0. Shift tables presenting the number and percentage of patients cross-tabulating NCI CTC grade at baseline to the worst grade after baseline through the study (including results from unscheduled visits) will be provided by treatment group for the As Treated population. For analytes that have NCI-CTCAE gradings for both low and high values, low and high will be summarized separately. In the shifts of low values, any high values will be classified as normal and the worst low grade will be summarized. And in the shifts of high values, any low values will be classified as normal and the worst high grade will be summarized.

| Haematology analyte | Low NCI CTC grade | High NCI CTC grade |
|---|---|---|
| Red Blood Cell Count | - | - |
| Haemoglobin | X | X |
| Haematocrit | - | - |
| White Blood Cell Count | X | X |
| Neutrophils (absolute) | X | - |
| Eosinophils (absolute) | - | X |
| Basophils (absolute) | - | - |
| Lymphocytes (absolute) | X | X |
| Monocytes (absolute) | - | - |
| Platelet count | X | - |

| Serum chemistry analyte | Low NCI CTC grade | High NCI CTC grade |
|---|---|---|
| ALT | - | X |
| AST | - | X |
| Alkaline phosphatase | - | X |
| GGT | - | X |
| LDH | - | X |
| Total bilirubin | - | X |
| Direct bilirubin | - | - |
| Glucose | X | - |
| Sodium | X | X |
| Potassium | X | X |
| Calcium (adjusted) | X | X |
| Magnesium | X | X |
| Blood urea nitrogen | - | - |
| Creatinine | - | X |
| Calculated creatinine clearance | - | - |
| CPK | - | X |
| Albumin | X | - |
| Amylase | - | X |
| Lipase | - | X |
| Procalcitonin | - | - |
| Troponin T | - | X |
| NT-pro-BNP | - | - |

For lymphocytes, neutrophils/lymphocytes ratio (NLR), ALT, CPK, Troponin T, NT-ProBNP, and procalcitonin, the median values together with the interquartile ranges will be plotted over time by treatment group and visit. Moreover, a spaghetti plot will also be used to represent the patient profile over time by treatment group.

### 7.7.4 Vital Signs

The following vital signs and $SpO_2$ at room air (%) by pulse oximetry will be listed and summarized by treatment group and visit.

- systolic and diastolic blood pressure (mmHg);
- pulse rate (beats/min);
- temperature (°C);
- respiration rate (breaths/min).

Vital signs and $SpO_2$ at room air (%) data and their changes from baseline will be summarized by visit using standard descriptive statistics by treatment group and overall plitidepsin for the As Treated population. The baseline value will be defined as last scheduled or unscheduled non-missing value collected prior to the first dose of the first study drug administration. Assessments carried out on day of first study

drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables

If more than 10% of the patients preform an unscheduled vital signs assessment at the same relative day to the start date of study treatment then the vital signs and $SpO_2$ at room air data will be also summarised at the specific relative day. In case of several unscheduled vital signs and $SpO_2$ at room air assessments at the same day we will use the worst result.

For the above summaries, the vital signs and $SpO_2$ at room air (%) assessed just before the start and immediately at the end of the plitidepsin infusion (for patients randomised to plitidepsin arms) will not be taken into account. These assessments will be summarized separately, the vital signs and $SpO_2$ at room air (%) assessed just before the start and immediately at the end of the plitidepsin infusion; and the change from the start to the end of the plitidepsin infusion (end of the plitidepsin infusion value – start of the plitidepsin infusion value) will be summarized by visit for the plitidepsin arms and overall plitidepsin using standard descriptive statistics for the As Treated population.

### 7.7.5 Electrocardiograms

The following quantitative ECG measurements will be taken in triplicates during the study:

- heart rate (beats/min);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia corrected QT (QTcF) interval (msec);

The average QTcF interval (msec) values and changes from baseline will be summarized by treatment group and overall plitidepsin, and by visit using standard descriptive statistics for the As Treated population.

The Baseline value will be defined as last scheduled or unscheduled non-missing value collected prior to the first dose of the first study drug administration. Assessments carried out on day of first study drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

In addition, the number and percentage of patients with a potentially clinically important ECG result defined as:

- Average QTcF interval value > 500 msec
- Change from baseline in QTcF interval > 30 msec

will be tabulated by treatment group and overall plitidepsin, and visit for the As Treated population.

Patients participating in the QTc substudy will have additional measurements by continuous 12-lead ECG automated monitoring over Days 1 to 3. The QTc substudy will be managed by a vendor (ERT - eResearchTechnology, Inc). The data analysis methods will be detailed in a separate statistical analysis plan and results will be reported separately.

### 7.7.6 Physical Examination

Clinically significant abnormalities identified from physical examination are recorded in the eCRF as Medical History, Sign and Symptom or Adverse Events as appropriate and will be listed and summarized as such (See Sections 7.4.1 [Medical History], 7.4.3 [Signs and Symptoms] and 7.7.2 [Adverse Events]).

Physical examination results (normal/abnormal) and details of abnormalities will be listed for each patient.

### 7.7.7 Other Safety Variables

The number and percentage of patients per Barthel index category will be tabulated by visit, treatment group and overall plitidepsin for the As Treated population.

Subgroup analysis of TEAE and clinically relevant laboratory tests will be performed by treatment group and overall plitidepsin based on the following prognostic factors of medical interest for the As Treated population:

- Sex: female or male
- Age at study entry: '18 to 39', '40 to 64' or '≥65 years'
- Race: Asian, black, white, or other
- Ethnic group: 'Hispanic or Latino' or 'Not Hispanic or Latino'
- Site location: each study site with more than 1/6 out of the randomised patients (ie, >33 randomised patients for the futility analysis and >101 randomised patients for the final analysis) will be considered as a group and the remaining study sites, ie, those study sites with less than 1/6 out of the randomised patients will be pooled together as a one single group.
- Previous COVID-19 vaccination status: 'Fully vaccinated', 'Non-fully vaccinated' or 'No vaccinated'
- SARS-CoV-2 viral load ($log_{10}$ copies/mL) at Day 1 before study drug administration: '< 4', [4-7] or '> 7'

- Time between onset date of COVID-19 symptoms and initiation of study treatment: '≤ 5 days', '6 - 10 days' or '> 10 days'
- Charlson Comorbidity index (as derived using the eCRF data): '0 – 1' or '> 1'
- Geographical Region: Europe or Rest of the World
- Body mass index (kg/m$^2$) at Screening: '< 30' or '≥ 30'
- Diabetes mellitus at Screening: 'None or diet controlled', 'Uncomplicated' or 'End-organ damage'
- Hypertension at Screening (defined as Hypertension [SMQ] in the Medical History form): Yes or No

Clinically significant chest abnormalities detected by chest examinations (computed tomography scan or x-ray) are recorded in the eCRF as Medical History, Sign and Symptom or Adverse Events as appropriate and will be listed and summarized as such (See Sections 7.4.1 [Medical History], 7.4.3 [Signs and Symptoms] and 7.7.2 [Adverse Events]).

Chest imaging results (normal/abnormal) and details of abnormalities will be listed for each patient.

## 7.8 Futility Analysis

The study may be terminated based on the conduct of a formal interim analysis of futility. Enrollment will not be temporarily halted while data for the interim analysis is being reviewed. In the case that the statistical stopping rule for futility is not met, the study will continue through planned completion. The interim analysis is planned as follows.

- A futility analysis of the primary efficacy endpoint will be performed when 33% of events (sustained withdrawal of supplementary oxygen) have been reached. This analysis will occur when the first 175 events have reached a sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period.
- The rho family of beta-spending functions (with $\rho$=1.18) will be used for the calculation of the stopping boundaries for futility in order to control type II error, the stopping boundaries for the futility analysis will be calculated with the actual number of patients available in the ITT population at that moment; if the number of events at the futility analysis is 116 in a pair comparison, the beta spending corrected p-value to reject the alternative hypothesis should be higher or equal than 0.4199 and this p-value is associated with a hazard ratio ≤ 1.0382. The conditional power at this moment will be also calculated.

- If the recommendation of the IDMC was to discontinue one of the plitidepsin dosing arms at this futility analysis following the stopping rules, the study will continue from that point on a 1:1 randomisation fashion until the completion of the remaining treatment arms (203 patients per arm and 353 events of sustained withdrawal of supplementary oxygen in total necessary to perform the final analysis). The patients still ongoing in the dropped arm would continue to be followed-up as per protocol and a Bonferroni-adjusted type I error rate of 1.25% will be kept for the comparison of the primary endpoint between the remaining plitidepsin arm and the control arm.
- After submission of protocol amendment v7, some regulatory agencies has requested the analysis of prior primary efficacy endpoint data based on protocol amendment v6. Consequently, at the futility analysis time, an exploratory analysis with the patients fulfilling the prior requirements will be performed.

  For the subset of patients with a pre-baseline (ie, in the prior month) Barthel Index ≥ 90, the percentage of patients who achieve complete recovery by Day 8 will be presented by treatment group and Clopper–Pearson 95% CI will be computed for the binomial proportion. In addition, the difference in the percentage of patients who achieve complete recovery by Day 8 between each dose of plitidepsin versus control arm will be presented for each dose of plitidepsin and the exact 95% CI will be computed for the difference in the percentage.

  Complete recovery by Day 8 will be defined as

  i. meeting categories 0 to 2 on the 11-point WHO Clinical Progression Scale [at date of discharge when discharge is before or on Day 8 visit, or after the date of discharge but before or on Day 8 visit],
  ii. having Barthel index > 90/100 at time of discharge [when discharge is before or on Day 8 visit], and
  iii. with no readmission [or death] due to COVID-19 related signs or symptoms through Day 31

  If discharge is after Day 8 visit then the patient will be considered as **No complete recovery by Day 8**.

  If the 11-point WHO Clinical Progression Scale is missing or patient doesn't meet categories 0 to 2 between the date of discharge when discharge is before or on Day 8 visit and the Day 8 visit then the patient will be considered as **No complete recovery by Day 8**.

If Barthel index at time of discharge is missing or ≤ 90/100 at time of discharge when discharge is before or on Day 8 visit then the patient will be considered as **No complete recovery by Day 8**.

If the 11-point WHO Clinical Progression Scale is between 0 and 2 and Barthel index is > 90 at time of discharge when discharge is before or on Day 8 however patient discontinues the study before Day 31, except due to death for any other reason than COVID-19 disease, then the patient will be considered as **No complete recovery by Day 8**.

The complete recovery by Day 8 rate between each dose of plitidepsin versus control arm will be analysed using a stratified logistic regression model. The model will be adjusted for the randomisation stratification factors, ie, Geographical Region (Europe vs. Rest of the World) and Charlson Comorbidity index (0-1 vs. >1) as derived using the eCRF data. The odds ratios, 95% CIs, and 2-sided p-values for the comparison of each dose of plitidepsin versus control arm will be presented.

The 2-sided p-values will be adjusted for multiplicity using the Hochberg step-up procedure to preserve the type 1 error rate in the comparison of each dose of plitidepsin versus control arm. The Hochberg step-up procedure will be implemented as following:

- Let $p_1 \leq p_2$ denote the ordered unadjusted 2-sided p-values with associated null hypotheses $H_{01}$ and $H_{02}$, where $H_{0i}$ = complete recovery by Day 8 rate in plitidepsin [1.5 mg or 2.5 mg] arm = complete recovery by Day 8 rate in control arm.
- Then we follow the next stepwise procedure:
  - If $p_2 \leq 0.05$, reject $H_{01}$ and $H_{02}$ stop; else continue
  - If $p_1 \leq 0.05/2$, reject $H_{01}$ and stop
- Adjusted 2-sided p-values will be calculated as:
  - $q_2 = p_2$
  - $q_1 = \min[2*p_1, q_2]$

The adjusted 2-sided p-values for multiplicity using the Hochberg step-up procedure will be also presented.

The primary efficacy analysis described above will be performed using the FAS population.

- To maintain continuous study integrity, analysis will be conducted by an independent team. The Tables, Figures and Listings required for the interim analysis will be created in a separate and restricted-access study area. The conditional power (probability) that the final study result will be statistically significant, given the data observed thus far and assuming the original

design effects for the remainder of the study will be calculated by the unblinded independent statistician or delegate and sent to the IDMC at the time of the interim analysis. The IDMC will consider the option of declaring futility based on the crossing of the futility boundary as well as conditional power. Details of the process for the interim analysis and the resulting controlled dissemination of interim analysis data will be detailed in the IDMC Charter document.

In addition, at the time when 30 patients have been treated per group with a 30 day follow-up, the IDMC Support Team will provide the IDMC Chairperson with unblinded information on the number of deaths and SAEs. Upon review of this data, if either the difference in the percentage of deaths or SAEs Grade ≥3 is at least 20% higher in any plitidepsin arm in comparison with the control arm, IDMC Chairperson will contact the other members of the IDMC and the clinical trial would be halted for a specific safety analysis by the IDMC if she/he deems it necessary.

The IDMC can ask for a temporary halt of the clinical trial at any time to better analyse any potential benefit/risk concern.

In addition to the above analysis, meetings for an IDMC data review may be scheduled to ensure proper safety assessment during enrollment and study conduct. Initially, proposed timelines for meeting frequency to review unblinded safety data will be as follows: the IDMC will develop a charter and establish criteria for when meetings are to occur, plus identify a time for the planned interim analysis of futility should this latter event fall outside the times of the reoccurring meetings. The IDMC review meetings will occur until database lock or at an earlier time deemed suitable by the IDMC. This meeting schedule may be modified based on the observed patient accrual rates or signals seen in the safety data.

# 8. Changes in Planned Analysis

Despite wording in Protocol that WHO score 0 requires a test with RNA undetected (which would be achieved with a PCR or similar test), as scarce cases have been reported, Pharma Mar is accepting negative antigen tests (which is a protein detection test, and not RNA detection test) qualifying for score of 0.

Recruitment was stopped due to slow recruitment before reaching the 33% of events by Pharma Mar decision and futility analysis was cancelled.

An exploratory analysis of the comparison of the primary efficacy endpoint between each dose of plitidepsin versus control arm receiving and not receiving the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir), will be performed.

An exploratory analysis of the prior primary efficacy endpoint based on protocol amendment v6 will be performed at the final analysis time due to some regulatory agencies request.

# 9. Data Issues

Not applicable.

# 10. References

1. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008 Jun;36(5):309-32. doi: 10.1016/j.ajic.2008.03.002. Erratum in: Am J Infect Control. 2008 Nov;36(9):655. PMID: 18538699.
2. UCLA. Advanced Research Computing. Statistical Methods and Data Analytics. [Internet]. Testing the proportional hazard assumption in Cox models. Available at: Testing the proportional hazard assumption in Cox models (ucla.edu). Accessed on March 29, 2022.
3. Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. Stat Med. 2011 Aug 30;30(19):2409-21.

# 11. Appendices

## Appendix 1: Document History

| Document Version, Status, Date | Summary/Reason for Changes |
|---|---|
| Version 4, Final, 21 Apr 2023 | To incorporate:<br>- Supportive analyses of the primary efficacy endpoint:<br>  o Bootstrap resampling analysis simulating the original sample size.<br>  o Extended definition of the primary efficacy endpoint to incorporate the information related to the oxygen supplementation status.<br>- Analysis of the percentage of patients with a reduction ≥ 2-log in viral load or undetectable viral load of SARS-CoV-2 on Day 8.<br>- Supportive analysis of the nosocomial infection using a wider definition.<br>- An exploratory analysis of the comparison of the primary efficacy endpoint between each dose of plitidepsin versus control arm receiving and not receiving the antiviral control arm.<br>- Cancellation of the futility analysis.<br>- Other minor clarifications/corrections |
| Version 3, Final, 01 Jul 2022 | To incorporate changes from protocol v7 |
| Version 2, Final, 20 Dec 2021 | To incorporate changes from protocol v6 |
| Version 1, Final, 28 May 2021 | Not applicable; the first version |

# Appendix 2: Charlson Comorbidity Index

This index is calculated by the sum of weights associated to co-morbidities and age:

- Conditions with a weight of 1:
  - myocardial infarction,
  - congestive heart failure,
  - peripheral vascular disease,
  - cerebrovascular disease,
  - dementia,
  - chronic pulmonary disease,
  - connective tissue disease,
  - ulcer disease,
  - mild liver disease,
  - diabetes.
- Conditions with a weight of 2:
  - hemiplegia,
  - moderate or severe renal disease,
  - diabetes with end organ damage
  - any malignancy.
- Conditions with a weight of 3:
  - Moderate or severe liver disease (e.g., cirrhosis with ascites)
- Conditions with a weight of 6:
  - Metastatic solid tumor oi AIDS
- Each decade of age over 40 adds 1 point to risk, ie,
  - Age between 50-59 years: add 1 point;
  - Age between 60-69 years: add 2 points;
  - Age between 70-79 years: add 3 points;
  - Age between 80-89 years: add 4 points;
  - Age between 90:99 years: add 5 points;
  - Age between 100-109 years: add 6 points

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## Reference

- M Charlson, TP. Szatrowski, .J Peterson, J Gold. "Validation of a combined comorbidity index". *J Clin Epidemiol* 1994; 47(11): 1245-51

# Appendix 3: Barthel Index for Functional Assessment

| | With help | Independent |
|---|---|---|
| 1. Feeding (if food needs to be cut = help) | 5 | 10 |
| 2. Moving from wheelchair to bed and return (includes sitting up in bed) | 5-10 | 15 |
| 3. Personal toilet (wash face, comb hair, shave, clean teeth) | 0 | 5 |
| 4. Getting on and off toilet (handling clothes, wipe, flush) | 5 | 10 |
| 5. Bathing self | 0 | 5 |
| 6. Walking on level surface<br>(or if unable to walk, propel wheelchair)<br>*score only if unable to walk | 10<br>0* | 15<br>5* |
| 7. Ascend and descend stairs | 5 | 10 |
| 8. Dressing (includes tying shoes, fastening fasteners) | 5 | 10 |
| 9. Controlling bowels | 5 | 10 |
| 10. Controlling bladder | 5 | 10 |

# Appendix 4: Schedule of Assessments

| Procedure | Screening Day 0-1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 (±1 day) | Day 9 | Day 10 | Day 15[22] (±1 day) | Day 31[23] (±3 days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent[1] | X | | | | | | | | | | | | |
| Selection criteria[2] | X | | | | | | | | | | | | |
| IWRS registration | X | X | | | | | | | | | | | X |
| Medical history | X | | | | | | | | | | | | |
| Vital signs[3] | X | X | X | X | X | X | X | X | X | | | | X |
| Demographics | X | | | | | | | | | | | | |
| Charlson Comorbidity Index | X | | | | | | | | | | | | |
| Physical examination | X* | X | X | X | X | | | | X | | | | X |
| Electrocardiogram[4] | X | X | | X | | | | | | | | | X |
| Haematology[5] | X | X | X | X | X | | | | X | | | | X |
| Serum chemistry[6] | X | X | X | X | X | | | | X | | | | X |
| Coagulation[7] | | X | X | X | X | | | | X | | | | X |
| Serological test (IgG) | | X | | | | | | | | | | | X |
| Immunology[8] | | X | X | X | X | | | | X | | | | X |
| COVID-19 screen[9] | X | | | | | | | | | | | | |
| COVID-19 viral load[10] | | X | | | | | | | X | | | | |
| Chest imaging[11] | | X | | | | | | | X | | | | X |
| Pregnancy test[12] | X | | | | | | | | | | | | |
| Clinical status[13] | X | X | X | X | X | X | X | X | X | | | X | X |
| Functional status[14] | X | | | | | | | | X | | | X | X |
| Adverse events/TEAEs[15] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications[16] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Dexamethasone treatment[17] | | X | X | X | X | X | X | X | X | X | X | | |
| Plitidepsin treatment[18] | | X | X | X | | | | | | | | | |
| Remdesivir treatment[19] | | X | X | X | X | X | | | | | | | |
| Favipiravir treatment[20] | | X | X | X | X | X | | | | | | | |
| Premedication[21] | | X | X | X | X | X | | | | | | | |

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BUN = blood urea nitrogen; COVID-19 = coronavirus disease 2019; CPK = creatine phosphokinase; CRP = C-reactive protein; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; IL = interleukin; IV = intravenous; IWRS = interactive web response systems; LDH = lactate dehydrogenase; NIH = National Institute of Health; NT-pro-BNP = N-terminal pro B-type natriuretic peptide; PCR = polymerase chain reaction; PO = orally; qPCR = quantitative polymerase chain reaction; QTcF = QT interval corrected using Fridericia's formula; TEAE = treatment-emergent adverse event; TNFα = tumour necrosis factor alpha.

*Body weight and height should be measured at screening.

1 **Informed consent**: Must be obtained before the patient undergoes any study-specific procedure
2 **Selection criteria**: Confirm that patient meets all inclusion criteria and none of the exclusion criteria
3 **Vital signs**: Temperature, sitting blood pressure, heart rate, respiratory rate, PaO2 (obtained either by arterial blood gas analyses or from saturation of oxygen ($SpO_2$) by pulse oximetry, and its respective $FiO_2$ to be measured at screening, on Days 1 to 3 just before start and end of each plitidepsin infusion (plitidepsin groups)/once daily on Days 1 to 3 (control group), further once daily while the patient is hospitalised, and on Days 8, and 31 (±3 days). To estimate the PaO2/FiO2 ratio, the required equation would be used for imputing PaO2 from SpO2, and the information on the oxygen delivery devices and oxygen flow prescribed would be utilised for imputation of FiO2.
4 **ECG**: QTcF prolongation to be assessed at screening and on Days 1, 3 (postinfusion), and 31 (±3 days), and any QTcF values >500 msec will be flagged as increasing the likelihood of the treatment being proarrhythmic (per ICH Guidance E14)
5 **Haematology**: RBC, haemoglobin, haematocrit, WBC with differential, platelet count. Testing to be performed by the local laboratory for screening and by central laboratory for on-study tests (tests performed within 24 hours of screening do not have to be repeated)
6 **Serum chemistry**: *Prestudy screening assessments*: ALT, AST, total bilirubin, sodium, potassium, calcium (albumin adjusted), magnesium, creatinine, calculated creatinine clearance (Cockcroft-Gault equation), CPK, and troponin (I or T according to local practice). *On study assessments*: ALT, AST, alkaline phosphatase, GGT, LDH, total bilirubin, direct bilirubin, glucose (fasting), sodium, potassium, calcium (albumin adjusted calculation), magnesium, blood urea nitrogen, creatinine, calculated creatinine clearance (Cockcroft-Gault equation), CPK, albumin, amylase, lipase, procalcitonin, troponin T (high sensitivity), and NT-pro-BNP. Note that testing to be performed by the local laboratory for screening and by central laboratory for on-study tests; tests performed within 24 hours of screening do not have to be repeated. All serum chemistry parameters will be measured at Day 1 prior to initiation of study treatment, once daily during hospitalisation, and at follow-up visits on Days 8 (±1 day) and 31 (±3 days); except, troponin T (high sensitivity), and NT-pro-BNP that will be measured on Day 1, Day 8 (±1 day), and Day 31 (±3 days).
7 **Coagulation**: D-dimer
8 **Immunology**: Proinflamatory biomarkers (CRP, ferritin, IL-1β, IL-6, IL-10, TNFα) in each study arm from baseline (Day 1 prior to start of the study treatment) to Day 4 and Days 8 (±1 day), 15 (±1 day) and 31 (±3 days).
9 **COVID-19 screen**: Qualitative PCR, antigen test to be performed by local laboratory, or any other validated method approved by the local health authority, from appropriate biological samples collected no more than 72 hours before study treatment on Day 1 for screening test to confirm COVID-19. In case more than one available, the more recent one will be selected.
10 **COVID-19 viral load**: Quantitative real-time reverse transcription polymerase-chain-reaction test (qRT-PCR) test to be performed by central laboratory from oro-nasopharyngeal exudate on Day 1 prior to initiating treatment and on Day 8 (±1 day).
11 **Chest imaging:** CT scan or x-ray will be done on Days 1, 8 (±1 day), and 31 (±3 days). Chest imaging performed within 48 hours of Day 1 is accepted and does not have to be repeated
12 **Pregnancy test**: Serum or urine pregnancy test for females of child-bearing potential, to be performed by local laboratory for screening
13 **Clinical Status**: Assessed using the 11-point WHO Clinical Progression Scale will be performed at screening, daily from Day 1 while hospitalised and on Days 8 (±1 day), 15 (±1 day), and 31 (±3 days), where 0= uninfected, no viral RNA detected; 1 = asymptomatic, viral RNA detected; 2 = symptomatic, independent; 3 = symptomatic, assistance needed; 4 = hospitalised, no oxygen therapy (if hospitalised for isolation only, record status as for ambulatory patient); 5 = hospitalised, oxygen by mask or nasal prongs; 6 = hospitalised, oxygen by NIV or high flow; 7 = intubation and mechanical ventilation, $pO_2/FIO_2 \geq 150$ or $SpO_2/FIO_2 \geq 200$; 8 = mechanical ventilation, $pO_2/FIO_2 < 150$ ($SpO_2/FIO_2 < 200$) or vasopressors; 9 = mechanical ventilation, $pO_2/FIO_2 < 150$ and vasopressors, dialysis or ECMO; 10 = dead.
14 **Functional Status**: Assessed by the Barthel index score (Appendix 3); the pre-baseline (ie, > 1 month prior to at screening ) functional status should be recorded, in addition to Day 1 prior to initiating study treatment , at hospital discharge, and on Days 8 (±1 day), 15 (±1 day), and 31 (±3 days).

15 **Treatment-emergent adverse events (TEAEs)**: TEAEs should be documented and recorded at each visit (ie, from initiation of study treatment on Day 1 through at least Day 31), grading severity assessed using National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) v5.0, and relationship to study treatment assessed by investigator judgement

16 **Concomitant medications**: Concomitant medications and treatments will be recorded for all patients from 28 days before the start of study treatment and through study Day 31 (±3 days). All COVID-19 vaccinations should be recorded, regardless when they were given, until the end of study.

17 **Dexamethasone treatment**: On all study arms, patients will receive dexamethasone phosphate 8 mg/day IV (equivalent to 6.6 mg dexamethasone base) on Days 1 to 3 (administered as a premedication in plitidepsin arms), following by dexamethasone phosphate 7.2 mg (equivalent to 6 mg/day dexamethasone base) PO/IV from Day 4 and up to a total cumulative dose of 60 mg of dexamethasone base (as per physician judgement according to patient clinical condition and evolution). The study allows up to a total cumulative dose of 60 mg of dexamethasone base (calculation of the total dose will also include corticosteroids administered within 72 hours before the start of the study treatment and dexamethasone administered as premedication).

18 **Plitidepsin treatment**: Plitidepsin 1.5 or 2.5 mg intravenous (IV) infusion for 60 minutes will be administered on Days 1 to 3. A 30 (±5)-minute window is allowed for the plitidepsin administration between each day, and plitidepsin should not be given earlier than 23.5 hours on Days 2 and 3 of previous day plitidepsin administration. No other antiviral agents to be administered during Days 1 to 3.

19 **Remdesivir treatment**: Consistent with local treatment guidelines, patients randomised to the control arm may receive remdesivir 200 mg IV on Day 1 followed by 100 mg/day IV on Days 2 to 5.

20 **Favipiravir treatment**: Consistent with local treatment guidelines, patients randomised to the control arm may receive favipiravir 1600 mg BID PO on Day 1, followed by 600 mg BID PO daily for 2 to 5 days.

21 **Premedication** (before plitidepsin infusion start): For prevention of plitidepsin-related infusion reactions, administration of the following premedications should be ideally completed 20 to 30-minutes before initiating the plitidepsin infusion and, exceptionally, up to 2 h before plitidepsin infusion start:

a) Palonosetron 0.25 mg IV (tropisetron 5 mg IV could be considered if palonosetron is not available)
b) Diphenhydramine hydrochloride 25 mg IV (or equivalent, such as dexchlorpheniramine maleate 5 mg)
c) Ranitidine 50 mg IV (or equivalent, such as famotidine 20 mg IV)
d) Dexamethasone phosphate 8 mg IV (equivalent to 6.6 mg of dexamethasone base)

Additionally, patients treated with plitidepsin must receive tropisetron 5 mg PO/IV on Days 4 and 5 if tropisetron 5 mg IV was administered on Days 1, 2, and 3. These premedications and postmedications should be recorded as concomitant medications.

22 **Day 15** procedures will be performed in remote or on-site visit.

23 **End of study visit:** all patients will undergo safety and efficacy follow-up assessments on Day 31 (±3 days) or earlier if patient withdraw from study.

**Note:** Central randomisation with IWRS system will be implemented using stratified permuted blocks to balance groups for stratification factors. Patients will be assigned to each arm at a 1:1:1 ratio. Baseline is Day 1 prior to start of the study treatment. Antiviral treatment to be used according to the approved product information in each country, different dosages could be used.

# Statistical Analysis Plan (SAP)/Initiation of Programming Approval Form

**Type of Approval (select one) :** ☒ **SAP** ☐ **Initiation of Programming**

| | | | |
|---|---|---|---|
| **Sponsor Name:** | Pharma Mar S.A. | | |
| **Sponsor Protocol/CIP ID:** | APL-D-003-20 | **Labcorp Study ID:** | 000000213894 |
| **SAP text filename:** | Neptuno-APL-D-003-20_SAP Final v3.0_01Jul2022 | **TFL shells filename:** | Neptuno-APL-D-003-20_SAP TFL Shells Final v3.0_01Jul2022 |
| **Version:** | 4.0 | **Date:** | 21Apr2023 |

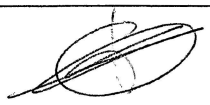
**Labcorp Approval(s):**

Lead Statistician

| | |
|---|---|
| Approval Signature<br>Print Name<br>Job Title<br>Date | DocuSigned by:<br>Igor Martin<br>Signer Name: Igor Martin<br>Signing Reason: I am the author of this document<br>Signing Time: 24 Apr 2023 \| 4:32:18 AM EDT<br>05C9C7F9B6424DE28D37E4685566C779 |

**Sponsor Approval(s):**

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

| | |
|---|---|
| Approval Signature<br>Print Name<br>Job Title<br>Date |  <br>ANTONIO NIETO<br>BIOSTATISTICS MANAGER<br>24APR2023 |

Please scan/email completed form(s) to the Lead Statistician listed below:

| | |
|---|---|
| **Printed Name/Title:** | Igor Martín/Principal Biostatistician |
| **Email:** | igor.martin@labcorp.com |

# Table, Figure, and Listing Shells

## A Phase 3, Multicentre, Randomised, Controlled Trial to Determine the Efficacy and Safety of Two Dose Levels of Plitidepsin Versus Control in Adult Patients Requiring Hospitalisation for Management of Moderate COVID-19 Infection

TFL Shells Status: Final
TFL Shells Version: 4.0
TFL Shells Date: 21APR2023

Investigational Product: Plitidepsin

Protocol Reference: APL-D-003-20
Labcorp Drug Development Study ID: 000000213894

Sponsor: Pharma Mar S.A.

Author:
Igor Martín, Principal Biostatistician

**Version History**

| Version Number | Date | Brief description of change |
|---|---|---|
| 4.0 | 21APR2023 | To incorporate changes from SAP v4.0 and amend some typos |
| 3.0 | 01JUL2022 | To incorporate changes from protocol v7 |
| 2.0 | 20DEC2021 | To incorporate changes from protocol v6 |
| 1.0 | 28MAY2021 | Initial version |

**TABLE OF CONTENTS**

# 1. INTRODUCTION

The table, figure, and listing (TFL) shells presented in this document are mock-ups and may be patient to minor format modifications once the actual data are used. The data represented in this document are used for example purposes only and do not reflect the actual study data captured. Significant changes related to the removal of data from the TFLs will be approved by the responsible Labcorp Drug Development project personnel and communicated to the sponsor.

The TFL shells are considered as a guideline for the statistical programmer(s) and statistician(s) who will produce the output.

# 2. GENERAL FORMAT GUIDELINES

## 2.1 General Programming Specifications

1. All programming of tables, figures and listings will be performed using the statistical software package SAS® version 9.4.

2. Contents (response) of variables will be presented as available in the database if there is no specific reason to change.

3. All pages will be numbered according to the table/figure/listing to which the page belongs to. The next table/figure/listing will be numbered from page 1 again.

4. When the study has no data for a particular TFL, the following sentence will be put in place of the table or listing: "No Data Available for This Report". The standard header/footer information will appear on these TLFs along with the required titles, but column headers will not be printed.

Pharma ABC Protocol: ABC-010-005 Version: Dry Run 1

**Table 14.1.2.2 Summary of Demographic Characteristics (All Randomized Set)**

No Data Available for This Report.

Program: /cvn/projects/prj/latephase/programs/000000123456/dev/tables/t_demo.sas
Output: /cvn/projects/prj/latephase/data/000000123456/tfl/prod/tables/t_14_01_02_02.rtf Run Date/Time: 01OCT2020 12:56 Page 1 of 1

## 2.2 Page Size and Layout

Labcorp Drug Development standards specified below will be used for TFLs.

| Item | Specification | | |
|---|---|---|---|
| | **Tables** | **Figures** | **Listings** |
| Language | UK English | UK English | UK English |
| Page Size | ☒ A4 ☐ Letter | ☒ A4 ☐ Letter | ☒ A4 ☐ Letter |
| Page orientation | ☒ Landscape<br>☐ Portrait | ☒ Landscape<br>☐ Portrait | ☒ Landscape<br>☐ Portrait |
| Output format | ☒ rtf ☐ xls ☐ pdf<br>☐ other:<br>_____ | ☒ rtf ☐ pdf<br>☐ other:<br>_____ | ☒ rtf ☐ xls ☐ pdf<br>☐ other:<br>_____ |

Page size margins:

| Margin | Landscape - A4 |
|---|---|
| Top | 3.00 cm |
| Bottom | 1.98 cm |
| Left | 3.81 cm |
| Right | 2.01 cm |
| From edge header | 3.00 cm |
| From edge footer | 1.48 cm |

## 2.3 Fonts

Font must be legible. The following is recommended:

- Font: Courier New
- Color: black
- Style:
  - regular for table/listing body
  - bold for titles and column headers
- Size:
  - 10 for titles (tables, listings, figures)
  - 9 for table body and column headers
  - 8 for listing body and footnotes

## 2.4 Titles

Up to 10 titles are available for tables, listings and figures. Standard title to be used in displays are specified below. The analysis set will appear in parentheses.

| Title | Left aligned | | |
|---|---|---|---|
| 1st | <<Sponsor>> | Protocol: <<Protocol ID>> | Version: <<Delivery type>> |
| 2nd | | | |
| 3rd | <<Table number Title>> (<<Analysis Set>>) | | |
| Further titles | << other titles e.g., subgroup titles>> | | |

Delivery type will be presented on each TFL as follows:

- DMC #1
- Dry Run #1
- Dry Run #2
- Final

## 2.5 Footnotes

Up to 10 footnotes are available for tables, listings and figures. Footnotes 9 and 10 are standard and are required for internal traceability. Footnotes 1 to 7 (left aligned) will be used as needed. Footnote 8 provides details on reference listings. Footnote 9 will contain program location and

name. Footnote 10 will contain the output location, name, run date/time and page number written in the format "Page x of y".

| Title | Left aligned |
|---|---|
| 1st – 7th | <<required explanatory footnotes/explanations> |
| 8th | Reference : Listing 16.XXX |
| 9th | <<Program location and name>> |
| 10th | <<Output location and name>> Run Date/Time: DDMMMYYYY HH:MM Page x of y |

## 2.6 Column Headings

Column headers will be presented this way:

- Bold case will be used
- For tables, the first column heading will be left aligned. The remaining column headings to be center aligned
- For listings, all column headings will be left aligned
- Treatment group will be included in all table column headers where treatment group is presented in the column
- Analysis Set count (N=XXX) will be included in all column headers where treatment group is presented in the column
- Summary statistic in column header will be included only if it is not included in the row headings
- An empty line below column headings will be added
- For sub-headings in the first column row header, 4 proceeding blank spaces will be used:

| **System Organ Class**<br>**Preferred Term** |
|---|

## 2.7 Text Capitalization and Spellings

All titles and column headers will be written with uppercase at the beginning of each word (excluding articles, prepositions, and conjunctions), except for acronyms, abbreviations and units.

Common abbreviations like LDL or WHO will be presented in uppercase. Units will be presented in mixed case as appropriate.

For text within the body of table outputs use sentence case. Exceptions to this are adverse event, concomitant/prior medications and/or medical history which will be presented as uppercase. For text within the body of listing outputs, use uppercase.

## 2.8 Presentation of Treatment Groups

The outputs will be presented by treatment group and the treatment description/labels to be used in the TFLs are defined in the table below:

| Treatment Code Number | Treatment Description | Long Treatment Label | Short Treatment Label |
|---|---|---|---|
| 1 | Plitidepsin 2.5mg | Plitidepsin 2.5mg | P 2.5mg |
| 2 | Plitidepsin 1.5mg | Plitidepsin 1.5mg | P 1.5mg |
| 3 | Control Arm | Control Arm | Control |
| 4 | Total | Total | Total |

For those outputs to compare the pooled plitidepsin arms versus control arm, the treatment description/labels to be used in the TFLs are defined in the table below:

| Treatment Code Number | Treatment Description | Long Treatment Label | Short Treatment Label |
|---|---|---|---|
| 1 | Pooled Plitidepsin Arms | Pooled Plitidepsin Arms | Plitidepsin |
| 2 | Control Arm | Control Arm | Control |

Long Treatment Labels will be used for treatment group presentations in the Tables/Figures/Listings. Only for special cases when space is limited, short format labels could be used.

## 2.9 Presentation of Time Points

**Time Points for Tables/Figures/Listings:**

The nominal visit names/labels and time point names/labels to be used in the Tables/Figures/Listings are defined in the table below:

| Visit Number | Visit Name | Visit Label | Time Point Name | Time Point Label |
|---|---|---|---|---|
| 1 | Screening Day 0-1 | Screening | | |
| 2 | Day 1 | Day 1 | Start of Infusion<br>End of Infusion | Start of Infusion<br>End of Infusion |
| 3 | Day 2 | Day 2 | Start of Infusion<br>End of Infusion | Start of Infusion<br>End of Infusion |
| 4 | Day 3 | Day 3 | Start of Infusion<br>End of Infusion | Start of Infusion<br>End of Infusion |
| 5 | Day 4 | Day 4 | | |
| 6 | Day 5 | Day 5 | | |
| 7 | Day 6 | Day 6 | | |
| 8 | Day 7 | Day 7 | | |
| 9 | Day 8 (±1 day) | Day 8 | | |
| 10 | Day 9 | Day 9 | | |
| 11 | Day 10 | Day 10 | | |
| 12 | Day 15 (±1 day) | Day 15 | | |
| 13 | Day 31 (±3 day) | Day 31 | | |

## 2.10 Presentation of Individual Data in the Listings

### 2.10.1 General

- The default sorting order for listings will be:
  - treatment group (as ordered in Section 2.8)
  - country alphabetically
  - ascending Site ID
  - ascending Patient ID
  - parameter/assessment (where applicable)
  - visit/assessment day (where applicable)
- Not repeat patients level data for multiple records per patient unless it moves out to the next page.
- One extra empty line will be included to separate patients where multiple lines per patient are presented.

### 2.10.2 Numeric Data

Individual raw (non-derived) data will be presented using the same rounding convention as that used in the Study Data Tabulation Models (SDTMs) for raw data, unless specifically stated otherwise.

Numeric data should be decimal aligned.

### 2.10.3 Character Data

Individual raw (non-derived) data will be presented as recorded in the SDTMs; thus, no changes (including any changes to letter casing) will be made for presentation in the listings.

Character data should be left aligned.

### 2.10.4 Date and time formats

In the listings original dates (not imputed) will be presented in the format ddMMMyyyy; two digits for the day (for example, 04, 25), three letters in capital for the month (for example, JAN) and four digits for the year (for example, 2003).

In the listings time will be presented in the format HH:MM.
Missing portions of dates and times will be presented on patient data listings as dashed.
For example:

| | | |
|---|---|---|
| December 15, 2003 | Complete date only | 15DEC2003 |
| December 15, 2003 Time 12 hours 34 minutes | Complete date/complete time | 15DEC2003/12:34 |
| December 15, 2003 Time 12 hours Unknown minutes | Complete date/unknown minutes | 15DEC2003/12:-- |
| December 15, 2003 Unknown hours 34 minutes | Complete date/unknown hours | 15DEC2003/--:34 |
| December 15, 2003 Unknown time | Complete date/unknown time | 15DEC2003/--:-- |
| December, 2003 | Unknown day | --DEC2003 |
| 2003 | Unknown month and day | -----2003 |
| Unknown date | Unknown date | --------- |

Dates that are missing because they are not applicable for the patient are output in the TFLs as "NA", unless otherwise specified.

Date/time variables should be right aligned.

## 2.11 Presentation of Summary Statistics and Statistical Analysis

### 2.11.1 Summary Statistics and Statistical Analysis Displays for continuous variables

Summary statistics for continuous variables will be displayed as follows:

| Presentation in Tables | Statistics | Description(s) |
|---|---|---|
| n | Count | Number of patients with valid observations |
| Mean (SD) | Mean and SD | Mean and SD will be displayed in one line as Mean (SD) with no blank spaces in the bracket and in cases where n=1, it will be displayed as Mean (-). |
| Median | Median | Median will be displayed in a single line. |
| Q1, Q3 | 25th Percentile, 75th Percentile | Q1 and Q3 will be displayed in one line as Q1, Q3 comma separated with one blank space. |
| Min, Max | Minimum, Maximum | Min and Max will be displayed in one line as min, max comma separated with one blank space. |

Inferential statistics will be displayed as follows:

| Presentation in Tables | Statistics | Description(s) |
|---|---|---|
| Adjusted Odds Ratio | Adjusted Odds Ratio | Adjusted Odds Ratio will be displayed in a single line. |
| 95% CI for Adjusted Odds Ratio | 95% Confidence Interval for Adjusted Odds Ratio | 95% Confidence Interval for Adjusted Odds Ratio will be displayed in one line as with dash and one blank space in between the values. |
| Hazard Ratio | Hazard Ratio | Hazard Ratio will be displayed in a single line. |
| 95% CI for Hazard Ratio | 95% Confidence Interval for Hazard Ratio | 95% Confidence Interval for Hazard will be displayed in one line as with dash and one blank space in between the values. |
| LS Mean (SE) | LS Mean and Standard Error | LS Mean and SE will be displayed in one line as LS Mean (SE) with no blank spaces in the bracket. |
| 95% CI for LS Mean | 95% Confidence Interval for LS means | 95% Confidence Interval for LS means will be displayed in one line as with dash and one blank space in between the values. |
| LS Mean Difference (SE) | LS Mean Difference and Standard Error | LS Mean Difference and SE will be displayed in one line as LS Mean Difference (SE) with no blank spaces in the bracket. |
| 95% CI for LS Mean Difference | 95% Confidence Interval for LS mean difference | 95% Confidence Interval for LS mean difference will be displayed in one line as with dash and one blank space in between the values. |
| 2-sided p-value | 2-sided p-value | 2-sided p-value will be displayed in a single line. |

| Statistics | Rounding rule |
|---|---|
| n | integer |
| mean | rounded to x+1 decimal places, where x is maximum number of decimal places in raw data |
| standard deviation | rounded to x+2 decimal places, where x is maximum number of decimal places in raw data |
| median | rounded to x+1 decimal places, where x is maximum number of decimal places in raw data<br>For Kaplan-Meier estimates, if median is not reached will be presented as "NR" |
| 25th percentile | rounded to x+1 decimal places, where x is maximum number of decimal places in raw data<br>For Kaplan-Meier estimates, if 25th percentile is not reached will be presented as "NR" |
| 75th percentile | rounded to x+1 decimal places, where x is maximum number of decimal places in raw data<br>For Kaplan-Meier estimates, if 75th percentile is not reached will be presented as "NR" |
| minimum | rounded to x decimal places, where x is maximum number of decimal places in raw data |
| maximum | rounded to x decimal places, where x is maximum number of decimal places in raw data |
| p-value | rounded using the SAS pvalue6.4 format<br>p-values of 0.0000 will be presented as "<0.0001"<br>p-values of 1.0000 will be presented as ">0.9999"<br>all p-values will be presented with a leading 0<br>p-values that cannot be estimated will be presented as "NE" |
| hazard ratio, odds ratio | rounded to 3 significant figures |
| survival rate | rounded to 3 significant figures |
| 95% CI | rounded to 3 significant figures |
| LS mean | rounded to x+1 decimal places, where x is maximum number of decimal places in raw data |

The rounding precision for the continuous laboratory parameters is provided in Appendix 1. Laboratory Tests – Precision Levels.

### 2.11.2 Summary Statistics Displays for categorical variables

For categorical variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category.

Categorical variables will be presented as follows:

| Statistics | Presentation/Rounding rule |
|---|---|
| number of patients with valid observations [n] | whole number; if n is 0 for categorical data, then n (%) statistic will be displayed as 0 |
| number of patients [N] | whole number |
| percentage of patients with valid observations [%] | Percentage values are to be rounded and presented to one decimal place, for example, 52.3. If the calculated percentage is > 0.0 but < 0.1 then < 0.1 is to be presented in the relevant table and/or listing. If the calculated percentage is 100 then present 100.0 in the relevant table and/or listing (i.e., to 1 decimal place) as this will ensure correct alignment. |

Percentages will be presented without % sign. Percentages will be displayed with one space between "n" and "(", e.g., 76 (16.5). No percentages will be presented for cases with 0 counts:

For any expected data in tables (e.g., demography, disposition), if the total number of patients in one category (e.g., Sex, Race or Age group etc.) is not equal to N, then a Missing category will be added. "Missing" cases will be included in the denominator. Where "Missing" cases are excluded from the denominator, details are provided on the relevant footnotes within the table.

Missing category will not be displayed if there are all 0's in a row.

**Table 12.1.2.1 Demographic Characteristics (Full Analysis Set)**

| | Placebo (N=20) n (%) |
|---|---|
| Race | |
| White | 2 ( 10.0) |
| Black | 0 |
| Asian | 8 ( 40.0) |
| Other | 5 ( 25.0) |
| Missing | 5 ( 25.0) |

For by-visit tables with categorical endpoints, patients who provide a missing / non-evaluable response but are still ongoing in the trial and attend the visit should be included in a Missing category.

Summary statistics for categorical variables will be aligned according to place values, i.e., line up units under units, tens under tens, etc.

## 2.12 Graphical Presentations

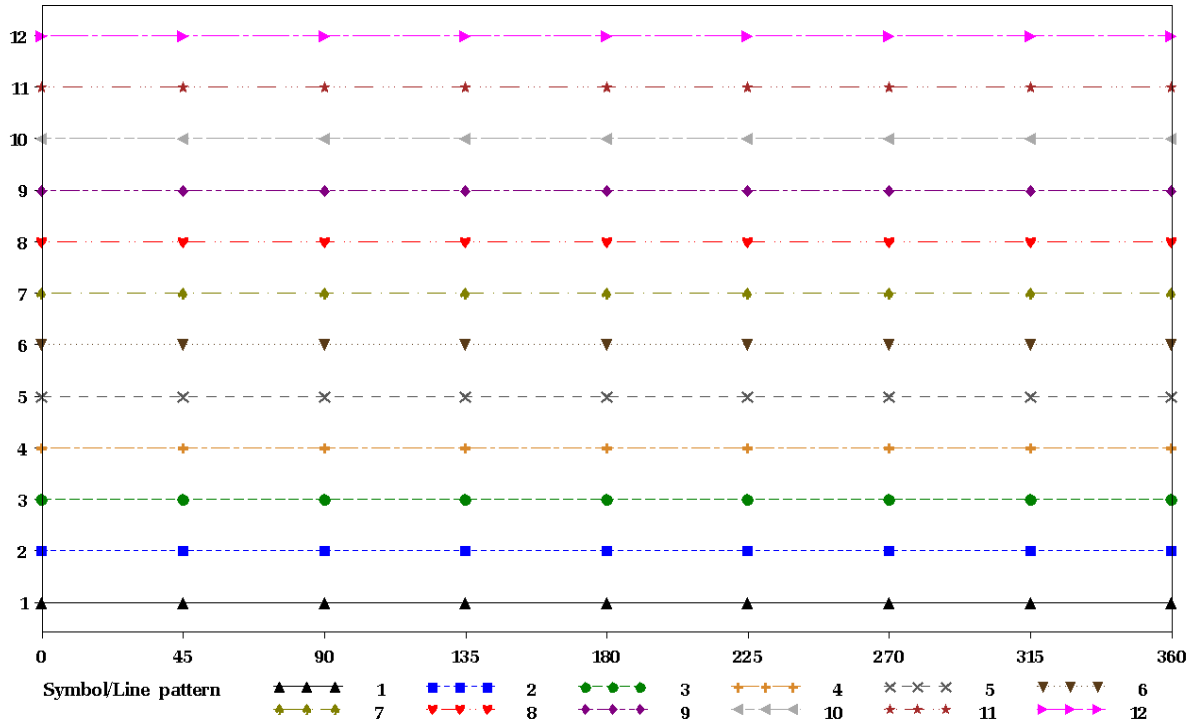
Figures will be presented in color. Abbreviations and symbols can be used in the figure due to space limitations. If used, they will be explained in the footnote under the figure.

The following symbols, color and patterns will be used:

| | Parameters for Symbol statement | | | | Parameters for Pattern statement | |
|---|---|---|---|---|---|---|
| | **font** | **value** | **color** | **line** | **color** | **value** |
| 1. | marker | C | black | 1 | black | L1 |

| | Parameters for Symbol statement | | | | Parameters for Pattern statement | |
|---|---|---|---|---|---|---|
| | **font** | **value** | **color** | **line** | **color** | **value** |
| 2. | marker | U | blue | 2 | blue | R1 |
| 3. | marker | W | green | 3 | green | X1 |
| 4. | marker | S | bio | 8 | bio | L2 |
| 5. | marker | X | dagr | 20 | dagr | R2 |
| 6. | marker | D | stbr | 33 | stbr | X2 |
| 7. | marker | O | olive | 41 | olive | L3 |
| 8. | marker | N | Red | 42 | red | R3 |
| 9. | marker | P | purple | 14 | purple | X3 |
| 10. | marker | A | darkgray | 30 | darkgray | L5 |
| 11. | marker | V | brown | 43 | brown | R5 |
| 12. | marker | B | magenta | 9 | magenta | X5 |

Such color/symbol/pattern scheme would result in the following presentation:




The order of the markers will match the order of the treatments, as defined in the statistical analysis plan (SAP).

## 2.13 Output Numbering

Numbering consistent with ICH E3 needs to be followed for numbering TFLs.

# 3. TABLES

## 3.1 Disposition

**Table 14.1.1.1 Patient Disposition (Screened Patients)**

| Study Disposition Reason | Plitidepsin 2.5mg n (%) | Plitidepsin 1.5mg n (%) | Control Arm n (%) | Total n (%) |
|---|---|---|---|---|
| Screened [a] | | | | xxx |
| Randomized | xxx (100.0) | xxx (100.0) | xxx (100.0) | xxx (100.0) |
| Treated | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Not Treated | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Completed the study | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Ongoing in the study | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Discontinued the Study | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Patient refusal (Withdrawal of Consent) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Study termination (clinical cut-off) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Lost To Follow-up | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Other | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

n = number of patients with data available; % = percentages are calculated based on the number of randomized patients as the denominator.
[a] Informed consent received.
Reference: Listing 16.2.1.1 and 16.2.1.2

*Programming notes (not part of the table):*

- *Table template TDS001.*
- *A "Missing" category should only be presented under the subcategories for Discontinued the Study where a reason for study discontinuation is missing.*
- *Ongoing in the study should be removed at the time of final reporting.*
- *Do not show percentage for "Screened" row.*

**Table 14.1.1.2 Analysis Sets (Intent-To-Treat Population)**

| Analysis Set | Plitidepsin 2.5mg (N=XXX) n (%) | Plitidepsin 1.5mg (N=XXX) n (%) | Control Arm (N=XXX) n (%) | Total (N=XXX) n (%) |
|---|---|---|---|---|
| Intent-To-Treat [a] | xxx (100.0) | xxx (100.0) | xxx (100.0) | xxx (100.0) |
| As Treated [b] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Full Analysis Set [c] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Per Protocol [d] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on the number of randomized patients as the denominator.
Patients within the Intent-To-Treat, Full Analysis Set and Per Protocol are counted according to the randomized treatment, whilst patients within the As Treated population are counted according to the actual treatment received.
[a] All randomised patients.
[b] All patients who received any exposure to the study drug (plitidepsin, dexamethasone, including for patients randomised to control arm, the regulatory-approved antiviral treatments, such as, remdesivir or favipiravir) during the study.
[c] All randomised patients who received at least 1 dose of study drug (plitidepsin, dexamethasone, including for patients randomised to control arm, the regulatory-approved antiviral treatments, such as, remdesivir or favipiravir) during the study and with at least 1 post-baseline clinical status collected.
[d] All patients in the FAS population who did not have any important protocol deviations that would interfere with the collection or interpretation of the efficacy.
Reference: Listing 16.2.3.1

*Programming notes (not part of the table):*

- *Table template TDS002.*
- *In case of patients assigned to the actual treatment received instead of the randomized treatment within the As Treated population, please update the second footnote which the patient numbers for those who are assigned to different treatment groups.*

**Table 14.1.1.3 Treatment Discontinuation (As Treated Population)**

| Treatment Disposition Reason | Plitidepsin 2.5mg (N=XXX) n (%) | Plitidepsin 1.5mg (N=XXX) n (%) | Control Arm (N=XXX) n (%) | Total (N=XXX) n (%) |
|---|---|---|---|---|
| Completed Treatment | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Ongoing Treatment | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Discontinued Treatment | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Primary Reason for Treatment Discontinuation | | | | |
| Adverse Event | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Patient's refusal of treatment | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Investigator's decision | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Other | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
Reference: Listing 16.2.1.1

*Programming notes (not part of the table):*

- *Table template TDS004.*
- *A "Missing" category should only be presented under the subcategories for Primary Reason for Treatment Discontinuation where a reason for treatment discontinuation is missing.*
- *Ongoing treatment should be removed at the time of final reporting.*
- *Cross check the patients with primary reason for treatment discontinuation = Adverse Event against patients with AEs with outcome = Discontinued Treatment. If there are discrepancies, consider adding a footnote referencing the patient numbers and known reason for difference.*

**Table 14.1.1.4 Screen Failures Prior to Randomization (Screened Patients)**

| Variable<br>Response | Total<br>(N=XXX)<br>n (%) |
|---|---|
| Screen Failure | |
| No | xxx (xxx.x) |
| Yes | xxx (xxx.x) |
| Primary Reason for Screen Failure | |
| Withdrawal of consent | xxx (xxx.x) |
| Participant deemed ineligible per the protocol-defined inclusion/exclusion criteria | xxx (xxx.x) |
| Other | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
Reference: Listing 16.2.1.2

*Programming notes (not part of the table):*

- *Table template TDS006.*

**Table 14.1.1.5 Number of Randomised Patients by Country and Site (Intent-To-Treat Population)**

| Country<br>Site | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) | Total<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Total | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Country 01>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Site 01>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Site 02>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Site 03>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Country 02>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Site 01>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Site 02>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| <<Site 03>> | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
Reference: Listing 16.2.1.1

*Programming notes (not part of the table):*

- *Table template TDS007.*

**Table 14.1.1.6 Summary of Stratification Factors (Intent-To-Treat Population)**

| Stratification Variable<br>Stratification Level [a]<br>Actual Stratification Level [b] | Plitidepsin 2.5mg (N=XXX)<br>n (%) | Plitidepsin 1.5mg (N=XXX)<br>n (%) | Control Arm (N=XXX)<br>n (%) | Total (N=XXX)<br>n (%) |
|---|---|---|---|---|
| Charlson Comorbidity index | | | | |
| Stratum: 0-1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: 0-1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: >1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Stratum: 2 or Greater | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: 0-1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: >1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Pre-baseline Barthel index | | | | |
| Stratum: <90 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: <90 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: ≥90 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Stratum: ≥90 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: <90 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Actual level: ≥90 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Geographical Region | | | | |
| Stratum: Europe | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Stratum: Rest of the World | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
[a] Stratification as per interactive response technology (IRT) system.
[b] Stratification as per eCRF.
Reference: Listing 16.2.1.3 and 16.2.1.5

*Programming notes (not part of the table):*

- *Table template TDS008.*

## 3.2 Protocol Deviations

**Table 14.1.1.7 Summary of Important Protocol Deviations Leading to Exclusion from Per Protocol Population (Intent-To-Treat Population)**

| Important Protocol Deviations | Plitidepsin 2.5mg (N=XXX) n (%) | Plitidepsin 1.5mg (N=XXX) n (%) | Control Arm (N=XXX) n (%) | Total (N=XXX) n (%) |
|---|---|---|---|---|
| Number of patients with at least 1 important deviation leading to exclusion from Per Protocol set [a] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Failure to complete or comply with inclusion/exclusion criteria | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Administration Use of prohibited medication | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
[a] Patients may have had more than 1 important protocol deviation.
Reference: Listing 16.2.2.2

*Programming notes (not part of the table):*

- *Table template TPD001.*

## 3.3 Demographics and Baseline Characteristics

**Table 14.1.2.1 Summary of Demographic Characteristics (Intent-To-Treat Population)**

| Characteristic<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) | Total<br>(N=XXX) |
|---|---|---|---|---|
| Age (years) | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Age Group (years), n (%) | | | | |
| >= 18 to 39 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 40 to 64 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 65 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Sex, n (%) | | | | |
| Male | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Female | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Child bearing potential, n (%) [a] | | | | |
| Yes | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| No, Surgically Sterile/Post Menopausal | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| No, Other | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
[a] Only females. Percentages are calculated based on the numer of females per group as the denominator.
[b] Patients with more than one race reported has been included in the Multiple category.
[c] Body mass index (kg/m^2) = body weight (kg) / height (m^2)
[d] Body surface area (m^2) = weight^0.425 (kg) × height^0.725 (cm) × 0.007184
Reference: Listing 16.2.4.1 and 16.2.4.2

**Table 14.1.2.1 Summary of Demographics Characteristics (Intent-To-Treat Population)**

| Characteristic<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) | Total<br>(N=XXX) |
|---|---|---|---|---|
| Race, n (%) [b] | | | | |
| American Indian or Alaska Native | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Asian | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Black or African American | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Native Hawaiian or Other Pacific Islander | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Multiple | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| White | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Other | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Not Hispanic or Latino | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Unknown | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Height at Screening (cm) | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
[a] Only females. Percentages are calculated based on the numer of females per group as the denominator.
[b] Patients with more than one race reported has been included in the Multiple category.
[c] Body mass index (kg/m^2) = body weight (kg) / height (m^2)
[d] Body surface area (m^2) = weight^0.425 (kg) × height^0.725 (cm) × 0.007184
Reference: Listing 16.2.4.1 and 16.2.4.2

**Table 14.1.2.1 Summary of Demographics Characteristics (Intent-To-Treat Population)**

| Characteristic<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) | Total<br>(N=XXX) |
|---|---|---|---|---|
| Weight at Screening (kg) | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Body Mass Index at Screening (kg/m^2) [c] | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Body Mass Index Group at Screening (kg/m^2) [c], n (%) | | | | |
| < 18.5 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 18.5 and < 25 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 25 and < 30 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 30 and < 35 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 35 and < 40 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| >= 40 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Body Surface Area at Screening (m^2) [d] | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
[a] Only females. Percentages are calculated based on the numer of females per group as the denominator.
[b] Patients with more than one race reported has been included in the Multiple category.
[c] Body mass index (kg/m^2) = weight (kg) / height (m^2)
[d] Body surface area (m^2) = weight^0.425 (kg) × height^0.725 (cm) × 0.007184

Reference: Listing 16.2.4.1 and 16.2.4.2

*Programming notes (not part of the table):*

- *Table template TDM001.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *A "Missing" category should only be presented under the subcategories for any categorical variable in case of missing data.*

**Table 14.1.3.1 Summary of Baseline Characteristics (Intent-To-Treat Population)**

| Characteristic<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) | Total<br>(N=XXX) |
|---|---|---|---|---|
| Chest Imaging at Enrolment, n (%) | | | | |
| Pulmonary Infiltrates | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Pleural Fluid | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Atelectasis | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Pulmonary Oedema | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Bilateral Pneumonia | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Lateral Pneumonia | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Other | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Systolic Blood Pressure (mmHg) at Screening | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Diastolic Blood Pressure (mmHg) at Screening | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |

*<continue for the following characteristics: pulse rate (beats/min) at Screening, temperature (C) at Screening, respiration rate (breaths/min) at Screening, and oxygen saturation at room air (%) at Screening>*

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Reference: Listing 16.2.4.2

*Programming notes (not part of the table):*

- *Table template TDM002.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *A "Missing" category should only be presented under the subcategories for any categorical variable in case of missing data.*

## 3.4 Medical History

**Table 14.1.3.2 Active Medical History by System Organ Class and Grouped Preferred Term (Intent-To-Treat Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) | Total<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Number of Patients with at Least one Active Medical History Record [b] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| System Organ Class 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| System Organ Class 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
[a] Within a system organ class, a patient may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Active medical conditions are those ticked on eCRF as Ongoing (with or without treatment).
Note: MedDRA version &meddra.
Reference: Listing 16.2.4.3

*Programming notes (not part of the table):*

- *Table template TMH001.*
- *Sort by Internationally Agreed Order system organ class and descending grouped preferred term in the total column. Includes all medical history.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *For uncoded medical histories present the verbatim term in place of the grouped preferred term in an 'Uncoded' system organ class.*

**Table 14.1.3.3 Past Medical History by System Organ Class and Grouped Preferred Term (Intent-To-Treat Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) | Total<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Number of Patients with at Least one Past Medical History Record [b] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| System Organ Class 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| System Organ Class 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
[a] Within a system organ class, a patient may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Past medical conditions are those not ticked on eCRF as Ongoing.
Note: MedDRA version &meddra.
Reference: Listing 16.2.4.3

*Programming notes (not part of the table):*

- *Table template TMH001.*
- *Sort by Internationally Agreed Order system organ class and descending grouped preferred term in the total column. Includes all medical history.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *For uncoded medical histories present the verbatim term in place of the grouped preferred term in an 'Uncoded' system organ class.*

## 3.5 Prior and Concomitant Medications

**Table 14.1.4.1 Summary of Prior Medications (Intent-To-Treat Population)**

| Therapeutic Subgroup<br>Chemical Subgroup<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) | Total<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Number of Patients with any Prior Medication | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 4 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 4 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
ATC = Anatomical Therapeutic Chemical, WHO = World Health Organization.
Notes: Prior medications are those taken prior to screening with a stop date prior to the first dose date of any study drug administration.
Prior medications were coded using WHODrug Global, &whodrug.
[a] Within a Chemical Subgroup, a patient may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each Chemical Subgroup.
Reference: Listing 16.2.4.4

*Programming notes (not part of the table):*

- *Table template TCM001.*
- *Sort by descending order of Anatomical Group, then descending order of Chemical Subgroup, then descending order of grouped preferred term in the total column. Where groups or terms tie these should be sorted alphabetically.*
- *Assign the version of WHO Drug Dictionary to &whodrug. macro variable as Format Bx, Version Month YYYY and update the version of WHO Drug Dictionary used for coding as needed.*
- *For coded medications with missing WHO ATC Level 4, present the WHO ATC Level 3 in place of the WHO ATC Level 4. If WHO ATC Level 3 is also missing, present WHO ATC Level 2 in place of the WHO ATC Level 4.*

**Table 14.1.4.2 Summary of Concomitant Medications, excluding COVID-19 Antiviral Therapies or Immunomodulatory Concomitant Medications (Intent-To-Treat Population)**

| Therapeutic Subgroup<br>Chemical Subgroup<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) | Total<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Number of Patients with any Concomitant Medication | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 4 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 4 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
ATC = Anatomical Therapeutic Chemical, WHO = World Health Organization.
Notes: Concomitant medications are those with a start date on or after the first dose date of any study drug administration, or those with a start date before the first dose date of any study drug administration and a stop date on or after the first dose date of any study drug administration or ongoing at the end of the study.
COVID-19 antiviral therapies or immunomodulatory concomitant medications are excluded from this table.
Concomitant medications were coded using WHODrug Global, &whodrug.
[a] Within a Chemical Subgroup, a patient may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each Chemical Subgroup.
Reference: Listing 16.2.4.5

*Programming notes (not part of the table):*

- *Table template TCM002.*
- *Sort by descending order of Anatomical Group, then descending order of Chemical Subgroup, then descending order of grouped preferred term in the total column. Where groups or terms tie these should be sorted alphabetically.*
- *Assign the version of WHO Drug Dictionary to &whodrug. macro variable as Format Bx, Version Month YYYY and update the version of WHO Drug Dictionary used for coding as needed.*
- *For coded medications with missing WHO ATC Level 4, present the WHO ATC Level 3 in place of the WHO ATC Level 4. If WHO ATC Level 3 is also missing, present WHO ATC Level 2 in place of the WHO ATC Level 4.*

**Table 14.1.4.3 Summary of COVID-19 Antiviral Therapies or Immunomodulatory Concomitant Medications (Intent-To-Treat Population)**

| Therapeutic Subgroup<br>Chemical Subgroup<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) | Total<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Number of Patients with any COVID-19 Antiviral Therapies or Immunomodulatory Concomitant Medication | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 4 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| WHO ATC Level 4 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 1 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grouped Preferred Term 2 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
ATC = Anatomical Therapeutic Chemical, WHO = World Health Organization.
Notes: Concomitant medications are those with a start date on or after the first dose date of any study drug administration, or those with a start date before the first dose date of any study drug administration and a stop date on or after the first dose date of any study drug administration or ongoing at the end of the study.
Only COVID-19 antiviral therapies or immunomodulatory concomitant medications are presented in this table.
Concomitant medications were coded using WHODrug Global, &whodrug.
[a] Within a Chemical Subgroup, a patient may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each Chemical Subgroup.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TCM002.*
- *Sort by descending order of Anatomical Group, then descending order of Chemical Subgroup, then descending order of grouped preferred term in the total column. Where groups or terms tie these should be sorted alphabetically.*
- *Assign the version of WHO Drug Dictionary to &whodrug. macro variable as Format Bx, Version Month YYYY and update the version of WHO Drug Dictionary used for coding as needed.*
- *For coded medications with missing WHO ATC Level 4, present the WHO ATC Level 3 in place of the WHO ATC Level 4. If WHO ATC Level 3 is also missing, present WHO ATC Level 2 in place of the WHO ATC Level 4.*

## 3.6 Signs and Symptoms

**Table 14.1.5.1 Summary of Signs and Symptoms (Intent-To-Treat Population)**

| Characteristic<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) | Total<br>(N=XXX) |
|---|---|---|---|---|
| Time between Onset Date of COVID-19 Symptoms and Initiation of Study Treatment (days) [a] | | | | |
| n | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx | xx, xx |
| History of Fever, n (%) | | | | |
| Yes | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| No | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Unknown | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Cough, n (%) | | | | |
| Yes, non-productive | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Yes, productive | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Yes, with haemoptysis | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| No | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Unknown | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

*<continue for the following signs and symptoms with the subcategories [Yes/No/Unknown]: sore throat, runny nose (rhinorrhoea), wheezing, shortness of breath, lower chest wall indrawing, chest pain, conjunctivitis, lymphadenopathy, headache, loss of smell (anosmia), loss of taste (ageusia), seizures, fatigue/malaise, anorexia, altered consciousness/confusion, muscle aches (myalgia), joint pain (arthralgia), inability to walk, abdominal pain, diarrhoea, vomiting/nausea, skin rash, bleeding (haemorrhage), and other symptom(s).>*

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
[a] Time between onset date of COVID-19 symptoms and initiation of study treatment (days) = (date of the first study drug administration - onset date of COVID-19 symptoms)
Reference: Listing 16.2.4.9

*Programming notes (not part of the table):*

- *Table template TDM002.*
- *A "Missing" category should only be presented under the subcategories for any Sign and Symptom in case of missing data.*

## 3.7 Primary Efficacy Endpoint

**Table 14.2.1.1.1 Time to Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients who Reported Sustained Withdrawal of Oxygen Supplementation, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Sustained Withdrawal of Oxygen Supplementation (days) 95% CI [a] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [b] | x.xxx | x.xxx | |
| 2-sided p-value adjusted for Multiplicity [b,c] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [d,e] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Stratified log-rank test p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.1.1.2 Time to Sustained Withdrawal of Oxygen Supplementation - Proportional Hazard Assumption and Restricted Mean Survival (Intent-To-Treat Population)**

| Variable | Time Dependent Covariate | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|---|
| p-value [a] | x.xxxx | | | |
| Restricted Mean Survival at Day 4 | | x.xxx | x.xxx | x.xxx |
| Restricted Mean Survival at Day 8 | | x.xxx | x.xxx | x.xxx |
| Restricted Mean Survival at Day 15 | | x.xxx | x.xxx | x.xxx |
| Restricted Mean Survival at Day 31 | | x.xxx | x.xxx | x.xxx |

N = number of patients in analysis set.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Time dependent covariate p-value calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and its time dependent covariate, i.e., treatment group*log(time). Censored patients at time 0 will not be used in the model.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If time dependent covariate p-value is <0.05 then restricted mean survival at Day 4, Day 8, Day 15 and Day 31 will be calculated. Otherwise, restricted mean survival at Day 4, Day 8, Day 15 and Day 31 will not be calculated and their rows will be removed from the table.*

**Table 14.2.1.1.3 Time to Sustained Withdrawal of Oxygen Supplementation - Sensitivity Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Sensitivity Analysis 1 - Unstratified Log-Rank Test | | | |
| 2-sided p-value [a] | x.xxx | x.xxx | |
| Sensitivity Analysis 2 - Unstratified Cox Regression Model | | | |
| Hazard Ratio [b,c] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [b,c] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [b] | x.xxx | x.xxx | |
| Sensitivity Analysis 3 - Stratified Log-Rank Test using the Investigator-Derived Values from IRT | | | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| Sensitivity Analysis 4 - Stratified Cox Regression Model using the Investigator-Derived Values from IRT | | | |
| Hazard Ratio [e,c] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [e,c] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [e] | x.xxx | x.xxx | |

N = number of patients in analysis set; CI = Confidence interval; IRT = Interactive Response Technology.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] 2-sided p-values calculated using an unstratified log-rank test with the fixed effect of the treatment group.
[b] Hazard Ratio, 95% CI and 2-sided p-values calculated using an unstratified Cox proportional-hazards regression model with the fixed effect of the treatment group. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[c] Statistics calculated relative to Control Arm.
[d] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as collected in IRT as covariates.
[e] Hazard Ratio, 95% CI and 2-sided p-values calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as collected in IRT as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Sensitivity Analysis 3 and 4 will be only presented if at least the 5% of the patients in any treatment group are mis-stratified.*

**Table 14.2.1.1.4 Time to Sustained Withdrawal of Oxygen Supplementation - Bootstrap Resampling Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Supportive Analysis – Bootstrap resampling | | | |
| Hazard Ratio [a,b] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [a,b] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [a] | x.xxx | x.xxx | |
| 2-sided p-value adjusted for Multiplicity [a,c] | x.xxx | x.xxx | |
| Percentage of samples with Hazard Ratio > 1 [a,b,d] | xx.x | xx.x | |
| Percentage of samples with 2-sided p-value < 0.025 [a,c,e] | xx.x | xx.x | |

N = number of patients in analysis set; CI = Confidence interval.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Hazard Ratio, 95% CI and 2-sided p-values calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and Bootstrap resampling simulating the original sample size (n=609 [203x3] and 10000 replications), median and percentiles for the CI are shown. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[b] Statistics calculated relative to Control Arm.
[c] Stratified Cox proportional-hazards regression p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Percentage of samples with Hazard Ratio > 1, calculated as the number of replications with Hazard Ratio > 1 / 10000 (replications) x 100%.
[e] Percentage of samples with 2-sided p-value < 0.025, calculated as the number of replications with 2-sided p-value adjusted for multiplicity < 0.025 / 10000 (replications) x 100%.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.1.1.5 Time to Sustained Withdrawal of Oxygen Supplementation - Adding Oxygen Supplementation Status Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Supportive Analysis – Adding Oxygen Supplementation Status | | | |
| Patients who Reported Sustained Withdrawal of Oxygen Supplementation, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Sustained Withdrawal of Oxygen Supplementation (days) 95% CI [a] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [b] | x.xxx | x.xxx | |
| 2-sided p-value adjusted for Multiplicity [b,c] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [d,e] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale or 'No supplemental oxygen needed' is recorded in the 'Vital Sign Oxygen status' form, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale or any oxygen supplementation is recorded in the 'Vital Sign Oxygen status' form)

[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Stratified log-rank test p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[e] Statistics calculated relative to Control Arm.

Reference: Listing 16.2.6.11

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

Repeat the Table 14.2.1.1.1 for the below tables and use the footnotes.

**Table 14.2.1.2 Time to Sustained Withdrawal of Oxygen Supplementation (Full Analysis Set)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Key secondary efficacy endpoints p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.1.3 Time to Sustained Withdrawal of Oxygen Supplementation (Per Protocol)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Key secondary efficacy endpoints p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.1.4 Complete Recovery by Day 8 as Defined in Protocol Amendment Version 6 (Full Analysis Set)***

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients with a pre-baseline Barthel Index ≥ 90 | xxx | xxx | xxx |
| Complete Recovery by Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI for Complete Recovery by Day 8 (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Complete Recovery by Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Complete Recovery by Day 8 (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Complete Recovery by Day 8 (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| 2-sided p-value adjusted for multiplicity [d,f] | x.xxx | x.xxx | |

N = number of patients in analysis set; n = number of patients in each category. % = percentages are calculated based on the number of patients with a pre-baseline Barthel Index ≥ 90 as the denominator.
CI = Confidence interval.
Notes: Complete recovery by Day 8 is defined as

i. meeting categories 0 to 2 on the 11-point WHO Clinical Progression Scale [at date of discharge when discharge is before or on D8 visit, or after the date of discharge but before or on D8 visit],
ii. having Barthel Index > 90/100 at time of discharge [when discharge is before or on Day 8 visit], and
iii. with no readmission [or death] due to COVID-19 related signs or symptoms through Day 31

[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Complete Recovery by Day 8 = Complete Recovery by Day 8 for the plitidepsin arm - Complete Recovery by Day 8 for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World) and Charlson Comorbidity Index (0-1 vs. >1) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm
[f] P-values adjusted for multiplicity using the Hochberg step-up procedure.
* Exploratory analysis of the prior primary efficacy endpoint based on protocol amendment v6 due to some regulatory agencies request.
Reference: Listing 16.2.6.1 and 16.2.6.2

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *This Table will be created only at the the time of the Futility Analysis.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

## 3.8 Key Secondary Efficacy Endpoints

**Table 14.2.2.1.1 Time to Sustained Hospital Discharge (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients who Reported Sustained Hospital Discharge, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Sustained Hospital Discharge (days) 95% CI [a] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [b] | x.xxx | x.xxx | |
| 2-sided p-value adjusted for Multiplicity [b,c] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [d,e] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient
i. discharges from the hospital, and
ii. has no subsequent re-admission
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Stratified log-rank test p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained hospital discharge than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.6

*Programming notes (not part of the table):*
- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

- *Last row from the stratified log-rank test, ie, 2-sided p-value adjusted for multiplicity, will be displayed only in the event that the primary efficacy endpoint of time to sustained withdrawal of oxygen supplementation is significant for both doses in the ITT population. In this case, the p-values for the key secondary efficacy endpoint will be adjusted for multiplicity using the Hochberg step-up procedure to preserve the type 1 error rate in the comparison of each dose of plitidepsin versus control arm.*

**Table 14.2.2.1.2 Time to Sustained Hospital Discharge - Sensitivity Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Sensitivity Analysis 1 - Unstratified Log-Rank Test | | | |
| 2-sided p-value [a] | x.xxx | x.xxx | |
| Sensitivity Analysis 2 - Unstratified Cox Regression Model | | | |
| Hazard Ratio [b,c] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [b,c] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [b] | x.xxx | x.xxx | |

N = number of patients in analysis set; CI = Confidence interval.
Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient
i. discharges from the hospital, and
ii. has no subsequent re-admission
[a] 2-sided p-values calculated using an unstratified log-rank test with the fixed effect of the treatment group.
[b] Hazard Ratio, 95% CI and 2-sided p-values calculated using an unstratified Cox proportional-hazards regression model with the fixed effect of the treatment group. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained hospital discharge than Control Arm.
[c] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.6

*Programming notes (not part of the table):*
- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

Repeat the Table 14.2.2.1.1 for the below table and use the footnotes.

**Table 14.2.2.2 Time to Sustained Hospital Discharge (Full Analysis Set)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient
i. discharges from the hospital, and
ii. has no subsequent re-admission
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Key secondary efficacy endpoints p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained hospital discharge than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.6

*Programming notes (not part of the table):*
- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.2.3 Time to Sustained Hospital Discharge (Per Protocol)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient
i. discharges from the hospital, and
ii. has no subsequent re-admission
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Key secondary efficacy endpoints p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained hospital discharge than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.6

*Programming notes (not part of the table):*
- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

## 3.9 Other Secondary Efficacy Endpoints

**Table 14.2.3.1 Clinical Status - 11-point WHO Clinical Progression Scale on Day 8 (Full Analysis Set)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| 11-point WHO Clinical Progression Scale on Day 8, n (%) (95% C.I.) [a] | | | |
| 0 = uninfected, no viral RNA detected | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 1 = asymptomatic, viral RNA detected | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 2 = symptomatic, independent | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 3 = symptomatic, assistance needed | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 4 = hospitalized, no oxygen therapy | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 5 = hospitalized, oxygen by mask or nasal prongs | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 6 = hospitalized, oxygen by NIV or high flow | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 7 = intubation and mechanical ventilation. pO2/FIO2 > 150 or SpO2/FIO2 > 200 | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 8 = mechanical ventilation pO2/FIO2 < 150 (SpO2/FIO2 < 200) or vasopressors | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 9 = mechanical ventilation pO2/FIO2 < 150 and vasopressors, dialysis, or ECMO | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| 10 = dead | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) | xxx (xx.x) (xx.x- xx.x) |
| Adjusted Odds Ratio [b,c] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [b,c] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [b] | x.xxx | x.xxx | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator.
CI = Confidence interval.
If the 11-point WHO scale at Discharge is assessed on the same date as the Day 8 visit, the 11-point WHO scale assessment at Discharge is used.
Otherwise, if an unscheduled assessment is also collected on the same date of the Day 8 visit, the worst 11-point WHO score is used.
[a] Goodman 95% confidence interval for multinomial proportions.
[b] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a proportional odds model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.1

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.2 Total Duration of Advanced Oxygen Support (Full Analysis Set)**

| Variable<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Patients who Required an Advanced Oxygen Support, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Duration of Advanced Oxygen Support (days) [a] | | | |
| n | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx |

N = number of patients in analysis set; n = number of patients in each category or with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Advanced oxygen support = high-flow nasal oxygen, non-invasive mechanical ventilation, invasive mechanical ventilation or ECMO.
[a] Duration of advanced oxygen support (days) = (date of last advanced oxygen support required - date of randomisation) + 1 - off-advanced oxygen support days.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*

- *Table template TEF001A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.3 Patients who Require ICU Admission per Period (Full Analysis Set)**

| Period<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require ICU Admission (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of ICU Admission Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of ICU Admission Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require ICU Admission (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of ICU Admission Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of ICU Admission Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require ICU Admission (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of ICU Admission Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of ICU Admission Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require ICU Admission (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require ICU Admission, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of ICU Admission Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of ICU Admission Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator; CI = Confidence interval; ICU = intensive care unit.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of ICU Admission Rate = ICU Admission Rate for the plitidepsin arm - ICU Admission Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.3

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.4 Re-Admission for COVID-19 Related Signs or Symptoms (Full Analysis Set)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients who Discharged from the Hospital | xxx | xxx | xxx |
| Re-admission for COVID-19 Related Signs or Symptoms, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI for Re-admission for COVID-19 Related Signs or Symptoms (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Re-admission for COVID-19 Related Signs or Symptoms, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |

N = number of patients in analysis set; n = number of patients in each category. % = percentages are calculated based on the number of patients who discharged from the hospital within each treatment group.
CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
Reference: Listing 16.2.6.3

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.5 Clinical Status - 11-point WHO Clinical Progression Scale on Days 4, 15, and 31 (Full Analysis Set)**

| Visit<br>11-point WHO Clinical Progression Scale | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Day 4, n (%) | | | |
| 0 = uninfected, no viral RNA detected | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 1 = asymptomatic, viral RNA detected | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 2 = symptomatic, independent | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 3 = symptomatic, assistance needed | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 4 = hospitalized, no oxygen therapy | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 5 = hospitalized, oxygen by mask or nasal prongs | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 6 = hospitalized, oxygen by NIV or high flow | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 7 = intubation and mechanical ventilation. pO2/FIO2 > 150 or SpO2/FIO2 > 200 | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 8 = mechanical ventilation pO2/FIO2 < 150 (SpO2/FIO2 < 200) or vasopressors | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 9 = mechanical ventilation pO2/FIO2 < 150 and vasopressors, dialysis, or ECMO | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 10 = dead | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| *<continue for the Day 15 and Day 31 visits>* | | | |

N = number of patients in analysis set; n = number of patients in each category. % = percentages are calculated based on N as the denominator.
If the 11-point WHO scale at Discharge is assessed on the same date as the Day 4, Day 15 or Day 31 visit, the 11-point WHO scale assessment at Discharge is used.
Otherwise, if an unscheduled assessment is also collected on the same date of the Day 4, Day 15 or Day 31 visit, the worst 11-point WHO score is used.
Reference: Listing 16.2.6.1

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.6.1 Patients who Require Oxygen Therapy (Full Analysis Set)**

| Timepoint<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Day 4 | | | |
| Patients at Day 4, n1 | xxx | xxx | xxx |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Day 8 | | | |
| Patients at Day 8, n1 | xxx | xxx | xxx |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| Day 15 | | | |
| Patients at Day 15, n1 | xxx | xxx | xxx |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| Day 31 | | | |
| Patients at Day 31, n1 | xxx | xxx | xxx |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | | | |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; n1 = number of patients with data available at timepoint; % = percentages are calculated based on n1 as the denominator; CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Oxygen Therapy Rate = Oxygen Therapy Rate for the plitidepsin arm - Oxygen Therapy Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.6.2 Patients who Require Oxygen Therapy per Period (Full Analysis Set)**

| Period<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Oxygen Therapy (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Oxygen Therapy, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Oxygen Therapy Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Oxygen Therapy Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator; CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Oxygen Therapy Rate = Oxygen Therapy Rate for the plitidepsin arm - Oxygen Therapy Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.7.1 Time to Intensification of Respiratory Support (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients who Reported Intensification of Respiratory Support through the Study, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Intensification of Respiratory Support (days) 95% CI [a] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [b] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [c,d] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [c,d] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [c] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Time to intensification of respiratory support (in days), defined as the first day, from randomisation through completion of the study, on which a patient satisfies a category > 6 on the 11-point WHO Clinical Progression Scale or dies due to any cause.
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer time to therapy intensification than Control Arm.
[d] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.10

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.7.2 Time to Intensification of Respiratory Support - Sensitivity Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Sensitivity Analysis 1 - Unstratified Log-Rank Test | | | |
| 2-sided p-value [a] | x.xxx | x.xxx | |
| Sensitivity Analysis 2 - Unstratified Cox Regression Model | | | |
| Hazard Ratio [b,c] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [b,c] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [b] | x.xxx | x.xxx | |

N = number of patients in analysis set; CI = Confidence interval.
Notes: Time to intensification of respiratory support (in days), defined as the first day, from randomisation through completion of the study, on which a patient satisfies a category > 6 on the 11-point WHO Clinical Progression Scale or dies due to any cause.
[a] 2-sided p-values calculated using an unstratified log-rank test with the fixed effect of the treatment group.
[b] Hazard Ratio, 95% CI and 2-sided p-values calculated using an unstratified Cox proportional-hazards regression model with the fixed effect of the treatment group. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[c] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.10

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

Repeat the Table 14.2.3.7.1 for the below table and use the footnotes.

**Table 14.2.3.7.3 Time to Intensification of Respiratory Support (Full Analysis Set)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Time to intensification of respiratory support (in days), defined as the first day, from randomisation through completion of the study, on which a patient satisfies a category > 6 on the 11-point WHO Clinical Progression Scale or dies due to any cause.
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer time to therapy intensification than Control Arm.
[d] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.10

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.8 Duration of ICU Stay (Full Analysis Set)**

| Variable<br>Statistic | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Patients who were Admitted in ICU, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Duration of ICU Stay (days) [a] | | | |
| n | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx |

N = number of patients in analysis set; n = number of patients in each category or with data available; % = percentages are calculated based on N as the denominator.
SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
ICU = intensive care unit.
[a] Duration of ICU stay (days) = (last date in ICU - date of admission in ICU) + 1 - off-ICU days.
Reference: Listing 16.2.6.3

*Programming notes (not part of the table):*

- *Table template TEF001A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.9.1 Patients who Require High-Flow Oxygen (Full Analysis Set)**

| Timepoint<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Day 4 | | | |
| Patients at Day 4, n1 | xxx | xxx | xxx |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Day 8 | | | |
| Patients at Day 8, n1 | xxx | xxx | xxx |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| Day 15 | | | |
| Patients at Day 15, n1 | xxx | xxx | xxx |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| Day 31 | | | |
| Patients at Day 31, n1 | xxx | xxx | xxx |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | | | |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; n1 = number of patients with data available at timepoint; % = percentages are calculated based on n1 as the denominator; CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of High-Flow Oxygen Rate = High-Flow Oxygen Rate for the plitidepsin arm - High-Flow Oxygen Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.9.2 Patients who Require High-Flow Oxygen per Period (Full Analysis Set)**

| Period<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require High-Flow Oxygen (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require High-Flow Oxygen, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of High-Flow Oxygen Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of High-Flow Oxygen Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator; CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of High-Flow Oxygen Rate = High-Flow Oxygen Rate for the plitidepsin arm - High-Flow Oxygen Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*
- *Table template TEF009A.*

**Table 14.2.3.10.1 Patients who Require Non-invasive Mechanical Ventilation (Full Analysis Set)**

| Timepoint<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Day 4 | | | |
| Patients at Day 4, n1 | xxx | xxx | xxx |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Day 8 | | | |
| Patients at Day 8, n1 | xxx | xxx | xxx |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| Day 15 | | | |
| Patients at Day 15, n1 | xxx | xxx | xxx |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| Day 31 | | | |
| Patients at Day 31, n1 | xxx | xxx | xxx |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | | | |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; n1 = number of patients with data available at timepoint; % = percentages are calculated based on n1 as the denominator; CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Non-invasive Mechanical Ventilation Rate = Non-invasive Mechanical Ventilation Rate for the plitidepsin arm - Non-invasive Mechanical Ventilation for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.10.2 Patients who Require Non-invasive Mechanical Ventilation per Period (Full Analysis Set)**

| Period<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Non-invasive Mechanical Ventilation (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Non-invasive Mechanical Ventilation, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | | | |
| Difference of Non-invasive Mechanical Ventilation Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Non-invasive Mechanical Ventilation Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator; CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Non-invasive Mechanical Ventilation Rate = Non-invasive Mechanical Ventilation Rate for the plitidepsin arm - Non-invasive Mechanical Ventilation for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*
- *Table template TEF009A.*

**Table 14.2.3.11.1 Patients who Require Invasive Mechanical Ventilation or ECMO (Full Analysis Set)**

| Timepoint<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| Day 4 | | | |
| Patients at Day 4, n1 | xxx | xxx | xxx |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Day 8 | | | |
| Patients at Day 8, n1 | xxx | xxx | xxx |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| Day 15 | | | |
| Patients at Day 15, n1 | xxx | xxx | xxx |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| Day 31 | | | |
| Patients at Day 31, n1 | xxx | xxx | xxx |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; n1 = number of patients with data available at timepoint; % = percentages are calculated based on n1 as the denominator; CI = Confidence interval; ECMO = extracorporeal membrane oxygenation.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Invasive Mechanical Ventilation or ECMO Rate = Invasive Mechanical Ventilation or ECMO Rate for the plitidepsin arm - Invasive Mechanical Ventilation or ECMO for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.11.2 Patients who Require Invasive Mechanical Ventilation or ECMO per Period (Full Analysis Set)**

| Period<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Require Invasive Mechanical Ventilation or ECMO (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Require Invasive Mechanical Ventilation or ECMO, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Invasive Mechanical Ventilation or ECMO Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator; CI = Confidence interval; ECMO = extracorporeal membrane oxygenation.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Invasive Mechanical Ventilation or ECMO Rate = Invasive Mechanical Ventilation or ECMO Rate for the plitidepsin arm - Invasive Mechanical Ventilation or ECMO for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.4

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.12.1 Time to Initiation with Immune-Modulating Drugs (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients who Started Subsequent Immune-Modulating Drugs through the Study, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Initiation with Immune-Modulating Drugs (days) 95% CI [a] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [b] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [c,d] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [c,d] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [c] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Time to initiation with immune-modulating drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent immune-modulating drugs.
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer time to therapy intensification than Control Arm.
[d] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.12.2 Time to Initiation with Immune-Modulating Drugs - Sensitivity Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Sensitivity Analysis 1 - Unstratified Log-Rank Test | | | |
| 2-sided p-value [a] | x.xxx | x.xxx | |
| Sensitivity Analysis 2 - Unstratified Cox Regression Model | | | |
| Hazard Ratio [b,c] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [b,c] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [b] | x.xxx | x.xxx | |

N = number of patients in analysis set; CI = Confidence interval.
Notes: Time to initiation with immune-modulating drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent immune-modulating drugs.
[a] 2-sided p-values calculated using an unstratified log-rank test with the fixed effect of the treatment group.
[b] Hazard Ratio, 95% CI and 2-sided p-values calculated using an unstratified Cox proportional-hazards regression model with the fixed effect of the treatment group. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[c] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

Repeat the Table 14.2.3.12.1 for the below table and use the footnotes.

**Table 14.2.3.12.3 Time to Initiation with Immune-Modulating Drugs (Full Analysis Set)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Time to initiation with immune-modulating drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent immune-modulating drugs.
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer time to therapy intensification than Control Arm.
[d] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.13.1 Time to Initiation with Antiviral Drugs (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients who Started Subsequent Antiviral Drugs through the Study, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Initiation with Antiviral Drugs (days) 95% CI [a] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [b] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [c,d] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [c,d] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [c] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Time to initiation with antiviral drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent antiviral drugs.
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer time to therapy intensification than Control Arm.
[d] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.13.2 Time to Initiation with Antiviral Drugs - Sensitivity Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Sensitivity Analysis 1 - Unstratified Log-Rank Test | | | |
| 2-sided p-value [a] | x.xxx | x.xxx | |
| Sensitivity Analysis 2 - Unstratified Cox Regression Model | | | |
| Hazard Ratio [b,c] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [b,c] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [b] | x.xxx | x.xxx | |

N = number of patients in analysis set; CI = Confidence interval.
Notes: Time to initiation with antiviral drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent antiviral drugs.
[a] 2-sided p-values calculated using an unstratified log-rank test with the fixed effect of the treatment group.
[b] Hazard Ratio, 95% CI and 2-sided p-values calculated using an unstratified Cox proportional-hazards regression model with the fixed effect of the treatment group. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[c] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

Repeat the Table 14.2.3.13.1 for the below table and use the footnotes.

**Table 14.2.3.13.3 Time to Initiation with Antiviral Drugs (Full Analysis Set)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Time to initiation with antiviral drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent antiviral drugs.
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer time to therapy intensification than Control Arm.
[d] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.14 Patients who Receive Subsequent Immune-Modulating Drugs per Period (Full Analysis Set)**

| Period<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Receive Sub. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Sub. Immune-Modulating Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Sub. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Sub. Immune-Modulating Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Sub. Immune-Modulating Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Receive Sub. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Sub. Immune-Modulating Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Sub. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Sub. Immune-Modulating Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Sub. Immune-Modulating Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Receive Subs. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Sub. Immune-Modulating Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Sub. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Sub. Immune-Modulating Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Sub. Immune-Modulating Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Receive Sub. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Sub. Immune-Modulating Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Sub. Immune-Modulating Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Sub. Immune-Modulating Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Sub. Immune-Modulating Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator; CI = Confidence interval; Sub. = Subsequent.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Subsequent Immune-Modulating Drugs Rate = Subsequent Immune-Modulating Drugs Rate for the plitidepsin arm - Subsequent Immune-Modulating Drugs Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.15 Patients who Receive Subsequent Antiviral Drugs per Period (Full Analysis Set)**

| Period<br>Variable | Plitidepsin 2.5mg<br>(N=XXX) | Plitidepsin 1.5mg<br>(N=XXX) | Control Arm<br>(N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Subsequent Antiviral Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Subsequent Antiviral Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Subsequent Antiviral Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Subsequent Antiviral Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Subsequent Antiviral Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Subsequent Antiviral Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Subsequent Antiviral Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Subsequent Antiviral Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Subsequent Antiviral Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Receive Subsequent Antiviral Drugs (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Non Receive Subsequent Antiviral Drugs, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Subsequent Antiviral Drugs Rate (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Subsequent Antiviral Drugs Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category; % = percentages are calculated based on N as the denominator; CI = Confidence interval.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Subsequent Antiviral Drugs Rate = Subsequent Antiviral Drugs Rate for the plitidepsin arm - Subsequent Antiviral Drugs Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.4.7

*Programming notes (not part of the table):*

- *Table template TEF009A.*

**Table 14.2.3.16.1 Patients with Nosocomial Infection per Period (Full Analysis Set)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Patients with Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI for Patients with Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Patients with Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI Patients with for Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Patients with Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI for Patients with Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Patients with Nosocomial Infection, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Patients with Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category. % = percentages are calculated based on N as the denominator.
CI = Confidence interval.
Notes: The lowest level terms that determine the 'Nosocomial infections' are 'Nosocomial infection' (preferred term: Nosocomial infection) and 'Nosocomial pneumonia' (preferred term: Pneumonia), based on MedDRA version &meddra.
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Nosocomial Infection Rate = Nosocomial Infection Rate for the plitidepsin arm - Nosocomial Infection Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *The final list of preferred terms that determine the 'Nosocomial infections' will be described in the 'Analysis Set Specification' document to ensure the latest MedDRA version is used for the analyses.*

**Table 14.2.3.16.2 Patients with Nosocomial Infection per Period – Using a Wider Definition (Full Analysis Set)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| From Day 1 to Day 4 | | | |
| Patients with Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI for Patients with Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| From Day 1 to Day 8 | | | |
| Patients with Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI Patients with for Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |
| From Day 1 to Day 15 | | | |
| Patients with Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI for Patients with Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

| | | | |
|---|---|---|---|
| From Day 1 to Day 31 | | | |
| Patients with Nosocomial Infection, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| 95% CI for Patients with Nosocomial Infection (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without Nosocomial Infection, n (%) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| Difference of Nosocomial Infection Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Nosocomial Infection Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |

N = number of patients in analysis set; n = number of patients in each category. % = percentages are calculated based on N as the denominator.
CI = Confidence interval.
Notes: Nosocomial infection defined as an infection that developed ≥ 48 hours after the admission or ≤ 7 days after the discharge, is symptomatic and/or requires treatment i.e., an antimicrobial therapy and/or a procedure (surgery, catheter removal etc).
[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Nosocomial Infection Rate = Nosocomial Infection Rate for the plitidepsin arm - Nosocomial Infection Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *The final list of adverse events or preferred terms that determine the wider definition of 'Nosocomial infections' will be described in the 'Analysis Set Specification' document to ensure the latest MedDRA version is used for the analyses.*

**Table 14.2.3.17.1 Overall Survival (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients who died due to any cause through the Study, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Overall Survival Estimate (days) 95% CI [a] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Mortality Rate by day (%) 95% Confidence Band [b] | | | |
| Day 4 | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Day 8 | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Day 15 | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Day 31 | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [c] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [d,e] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Overall survival defined as the time from randomisation to death due to any cause. Overall survival (days) = (date of death or censoring - date of randomisation + 1).
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] Calculated using the Kaplan-Meier estimator. Confidence bands derived based on Hall-Wellner method.
[c] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and the levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer survival than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.17.2 Overall Survival - Sensitivity Analysis (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Sensitivity Analysis 1 - Unstratified Log-Rank Test | | | |
| 2-sided p-value [a] | x.xxx | x.xxx | |
| Sensitivity Analysis 2 - Unstratified Cox Regression Model | | | |
| Hazard Ratio [b,c] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [b,c] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [b] | x.xxx | x.xxx | |

N = number of patients in analysis set; CI = Confidence interval.
Notes: Overall survival defined as the time from randomisation to death due to any cause. Overall survival (days) = (date of death or censoring - date of randomisation + 1).
[a] 2-sided p-values calculated using an unstratified log-rank test with the fixed effect of the treatment group.
[b] Hazard Ratio, 95% CI and 2-sided p-values calculated using an unstratified Cox proportional-hazards regression model with the fixed effect of the treatment group. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[c] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

Repeat the Table 14.2.3.17.1 for the below table and use the footnotes.

**Table 14.2.3.17.3 Overall Survival (Full Analysis Set)**

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Overall survival defined as the time from randomisation to death due to any cause. Overall survival (days) = (date of death or censoring - date of randomisation + 1).
[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] Calculated using the Kaplan-Meier estimator. Confidence bands derived based on Hall-Wellner method.
[c] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and the levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio < 1 favours a Plitidepsin arm to be associated with a longer survival than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.7

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.3.18 Change in SARS-CoV-2 viral load ($log_{10}$ copies/mL) (Full Analysis Set)**

| Visit<br>Variable<br>Statistic | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Day 1 | | | |
| Actual Value | | | |
| n | xxx | xxx | xxx |
| Mean (SD) | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) |
| Median | xxx.xxx | xxx.xxx | xxx.xxx |
| Q1, Q3 | xx.xxx, xx.xxx | xx.xxx, xx.xxx | xx.xxx, xx.xxx |
| Min, Max | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Day 8 | | | |
| Actual Value | | | |
| N | xxx | xxx | xxx |
| Mean (SD) | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) |
| Median | xxx.xxx | xxx.xxx | xxx.xxx |
| Q1, Q3 | xx.xxx, xx.xxx | xx.xxx, xx.xxx | xx.xxx, xx.xxx |
| Min, Max | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Change from Day 1 | | | |
| N | xxx | xxx | xxx |
| Mean (SD) | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) |
| Median | xxx.xxx | xxx.xxx | xxx.xxx |
| Q1, Q3 | xx.xxx, xx.xxx | xx.xxx, xx.xxx | xx.xxx, xx.xxx |
| Min, Max | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| LS Mean (SE) [a] | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) |
| 95% CI for LS Mean [a] | xxx.xxxx-xxx.xxxx | xxx.xxxx-xxx.xxxx | xxx.xxxx-xxx.xxxx |
| LS Mean Difference compared to Control Arm (SE) [a, b] | xxxx.xxx (xxx.xxxx) | xxxx.xxx (xxx.xxxx) | |
| 95% CI for LS Mean Difference compared to Control Arm [a, b] | xxx.xxxx-xxx.xxxx | xxx.xxxx-xxx.xxxx | |
| 2-sided p-value [a] | x.xxxx | x.xxxx | |

N = number of patients in analysis set; n = number of patients with data available.
CI = Confidence interval; LS = Least squares; SD = Standard deviation; Q1 =25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum; SE = Standard Error.
Any individual SARS-CoV-2 viral load values below the lower limit of quantification (<LLOQ) are treated as LLOQ/2 for the purpose of summary statistics.
[a] LS means, SEs, 95% CI and p-values are from an analysis of covariance (ANCOVA) model with fixed effects of treatment group, continuous SARS-CoV-2 viral load at Day 1, and categorical randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[b] Difference is calculated as LS Mean in Plitidepsin 2.5mg - LS Mean in Control Arm or LS Mean in Plitidepsin 1.5mg - LS Mean in Control Arm.

Reference: Listing 16.2.6.8

*Programming notes (not part of the table):*

- *Table template TEF001A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.19.1 Patients with Undetectable SARS-CoV-2 Viral Load on Day 8 (Full Analysis Set)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients with Undetectable SARS-CoV-2 Viral Load on Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI Patients with Undetectable SARS-CoV-2 Viral Load on Day 8 (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients with Detectable or Missing SARS-CoV-2 Viral Load on Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Detectable SARS-CoV-2 Viral Load on Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Missing SARS-CoV-2 Viral Load on Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Undetectable SARS-CoV-2 Viral Load Rate on Day 8, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Undetectable SARS-CoV-2 Viral Load Rate on Day 8 (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set; n = number of patients in each category. % = percentages are calculated based on N as the denominator.
CI = Confidence interval.
[a] Clopper–Pearson 95% confidence interval.
[b] Difference of Undetectable SARS-CoV-2 Viral Load Rate = Undetectable SARS-CoV-2 Viral Load Rate for the plitidepsin arm - Undetectable SARS-CoV-2 Viral Load Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm
Reference: Listing 16.2.6.8

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.19.2 Patients with a Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load on Day 8 (Full Analysis Set)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients with a Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load on Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI Patients with a Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load on Day 8 (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients with Detectable and a Reduction < 2-log in Viral Load or Missing SARS-CoV-2 Viral Load on Day 8, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load Rate on Day 8, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load Rate on Day 8 (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set; n = number of patients in each category. % = percentages are calculated based on N as the denominator.
CI = Confidence interval.
[a] Clopper–Pearson 95% confidence interval.
[b] Difference of Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load Rate = Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load Rate for the plitidepsin arm - Reduction ≥ 2-log in Viral Load or Undetectable SARS-CoV-2 Viral Load Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm
Reference: Listing 16.2.6.8

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.20 Summary of Proinflammatory Biomarkers - Change from Baseline (Full Analysis Set)**

Parameter (unit)

| Visit / Statistic | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|
| | Value at Visit | % Change from Baseline | Value at Visit | % Change from Baseline | Value at Visit | % Change from Baseline |
| Baseline | | | | | | |
| n | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| <<Day X>> | | | | | | |
| n | xxx | xxx | Xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Notes: The Baseline value for the proinflammatory biomarkers is defined as the value collected at the time of the clinic visit on Day 1.
For IL-1β, IL-6, IL-10, and TNFα: % change from Baseline = 100*(post-Baseline value - Baseline value)/Baseline Value
For CRP and ferritin, values are referred to the upper limit of normal (ULN): % change from Baseline = 100*((post-Baseline value/ULN) - (Baseline value/ULN))/(Baseline Value/ULN)
Reference: Listing 16.2.8.1.3

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *Parameters are: CRP, ferritin, IL-1β, IL-6, IL-10, and TNFα.*
- *Visits: Day 2, Day 3, Day 4, Day 8, and Day 31.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.21.1 Patients with a Serologic Response Anti-SARS-CoV-2 (Full Analysis Set)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm (N=XXX) |
|---|---|---|---|
| Patients at Day 31 with serologic assessment, n1 | xxx | xxx | xxx |
| Patients with a Serologic Response Anti-SARS-CoV-2, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% CI Patients with a Serologic Response Anti-SARS-CoV-2 (%) [a] | xx.x – xx.x | xx.x – xx.x | xx.x – xx.x |
| Patients without a Serologic Response Anti-SARS-CoV-2, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Difference of Serologic Response Anti-SARS-CoV-2 Rate, n (%) [b] | xx.x | xx.x | |
| 95% CI for Difference of Serologic Response Anti-SARS-CoV-2 Rate (%) [c] | xx.x – xx.x | xx.x – xx.x | |
| Adjusted Odds Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Adjusted Odds Ratio [d,e] | x.xxx - x.xxx | x.xxx - x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set; n = number of patients in each category; n1 = number of patients with data available at timepoint; % = percentages are calculated based on n1 as the denominator; CI = Confidence interval.
Notes: Serologic Response Anti-SARS-CoV-2:

- Baseline IgG Antibodies quantification is interpreted as negative (e.g. <0.8), borderline (e.g. ≥0.8 and <1.1) or missing and increases above the established boundary (e.g. ≥1.1), following study drug administration.
- Baseline IgG Antibodies are positive and the result at Day 31 sample is at least two-folds greater than the baseline sample.

[a] Clopper-Pearson 95% confidence interval.
[b] Difference of Serologic Response Anti-SARS-CoV-2 Rate = Serologic Response Anti-SARS-CoV-2 Rate for the plitidepsin arm - Serologic Response Anti-SARS-CoV-2 Rate for control arm.
[c] Exact 95% confidence interval.
[d] Adjusted Odds Ratio, 95% CI and 2-sided p-values based on a stratified logistic regression model with fixed effects of treatment group and randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[e] Statistics calculated relative to Control Arm
Reference: Listing 16.2.6.9

*Programming notes (not part of the table):*

- *Table template TEF009A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.21.2 Summary of anti-SARS-CoV-2 IgG - Change from Baseline (Full Analysis Set)**

| | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|
| Visit<br>Statistic | Value at Visit | % Change from Baseline | Value at Visit | % Change from Baseline | Value at Visit | % Change from Baseline |
| Baseline | | | | | | |
| n | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| Day 31 | | | | | | |
| n | xxx | xxx | Xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Notes: The Baseline value for the serologic response anti-SARS-CoV-2 is defined as the IgG Antibodies quantification value collected at the time of the clinic visit on Day 1.
% change from Baseline = 100*(Day 31 value - Baseline value)/Baseline Value
Reference: Listing 16.2.6.9

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.2.3.22 Time to Sustained Withdrawal of Oxygen Supplementation - Pooled Plitidepsin Arms (Intent-To-Treat Population)**

| Variable | Pooled Plitidepsin Arms (N=XXX) | Control Arm (N=XXX) |
|---|---|---|
| Patients who Reported Sustained Withdrawal of Oxygen Supplementation, n (%) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) |
| Time-to Sustained Withdrawal of Oxygen Supplementation (days) 95% CI [a] | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | |
| 2-sided p-value [b] | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | |
| Hazard Ratio [d,e] | x.xxx | |
| 95% CI for Hazard Ratio [d,e] | x.xxx – x.xxx | |
| 2-sided p-value [d] | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[b] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[c] Stratified log-rank test p-values adjusted for multiplicity using the Hochberg step-up procedure.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

## 3.10 Exploratory Analysis

**Table 14.2.4.1 Time to Sustained Withdrawal of Oxygen Supplementation - Multivariate Analysis (Intent-To-Treat Population)**

| Variable | Parameter Estimate | Standard Error | p-value | Hazard Ratio |
|---|---|---|---|---|
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |

Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Parameter Estimate, Standard Error, p-value, and Hazard Ratio based on a Cox proportional-hazards regression model with treatment group, randomisation stratification factors, ie, geographical region (Europe, Rest of the World), Charlson Comorbidity Index (0 - 1, > 1) and pre-baseline Barthel index (≥ 90 versus < 90) as derived using the eCRF data, and patients included before and after amendment (Protocol v.6 or before, Protocol v.7), sex (female, male), age at study entry (18 to 39, 40 to 64, ≥ 65 years), race (asian, black, white, other), ethnic group (Hispanic or Latino, Not Hispanic or Latino), site location (Site XXX, Site XXX, Other Sites), use of antiviral therapies or immunomodulatory drugs through the study (Yes, No), previous COVID-19 vaccination status (Fully vaccinated, Non-fully vaccinated, No vaccinated), anti-SARS-CoV-2 IgG at Day 1 (Non-positive, Positive), pre-randomisation dexamethasone (Yes, No), total duration of corticoid therapy (< 9 days, [9 – 11] days, > 11 days), total cumulative dose of corticoid therapy (dexamethasone or equivalent) (≤ 60 mg, > 60 mg), SARS-CoV-2 viral load (log10 copies/mL) at Day 1 before study drug administration (< 4, [4 - 7], > 7), time between onset date of COVID-19 symptoms and initiation of study treatment (≤ 5 days, 6 - 10 days, > 10 days), body mass index (kg/m2) at Screening (< 30, ≥ 30), hypertension at Screening (Yes, No), myocardial infarction (Yes, No), congestive heart failure (Yes, No), peripheral vascular disease (Yes, No), cerebrovascular disease (Yes, No), dementia (Yes, No), chronic obstructive pulmonary disease (Yes, No), connective tissue disease (Yes, No), peptic ulcer disease (Yes, No), liver disease (None, Mild, Moderate or Severe), diabetes mellitus (None or diet controlled, Uncomplicated, End-organ damage), hemiplegia (Yes, No), moderate or severe chronic kidney disease (Yes, No), solid tumor (None, Localized, Metastatic), leukemia (Yes, No), lymphoma (Yes, No), AIDS (Yes, No), ISARIC-4C mortality score (Low (0 - 3), Intermediate (4 - 8), High (9 - 14), Very high (≥ 15)), ISARIC-4C deterioration probability (≤ 25, (25 - 50], > 50), LDH at Baseline (≤ ULN, > ULN), CRP (mg/L) at Baseline (≤ 100, > 100), D-dimer at Baseline (≤ ULN, > ULN), ferritin at Baseline (≤ ULN, > ULN), creatinine at Baseline (≤ ULN, > ULN), IL-6 at Baseline (≤ Median, > Median), IL-10 at Baseline (≤ Median, > Median), lymphocytes count decreased at Baseline (Grade 0, Grade ≥ 1), neutrophils/lymphocytes ratio at Baseline (< 6, ≥ 6) and SARS-CoV-2 variant (Alpha, Beta, Gamma, Delta, Eta, Iota, Kappa, Lambda, Mu, any potential new variant) as covariates. Those covariates with more than 10% of missing values are omitted. A stepwise selection model is used, with significant level equal to 0.2 and 0.05, to enter into the model and to remain in the model, respectively.

*Programming notes (not part of the table):*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Omit those covariates with more than 10% of missing values from the multivariate analysis.*
- *Force to include the treatment arm in addition to the significant covariates.*

**Table 14.2.4.2 Time to Sustained Hospital Discharge - Multivariate Analysis (Intent-To-Treat Population)**

| Variable | Parameter Estimate | Standard Error | p-value | Hazard Ratio |
|---|---|---|---|---|
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |
| XXXXXXXXXXXXXXXXX | x.xxxx | x.xxxx | x.xxxx | x.xxx |

Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient

i. discharges from the hospital, and
ii. has no subsequent re-admission

[a] Parameter Estimate, Standard Error, p-value, and Hazard Ratio based on a Cox proportional-hazards regression model with treatment group, randomisation stratification factors, ie, geographical region (Europe, Rest of the World), Charlson Comorbidity Index (0 - 1, > 1) and pre-baseline Barthel index (≥ 90 versus < 90) as derived using the eCRF data, and patients included before and after amendment (Protocol v.6 or before, Protocol v.7), sex (female, male), age at study entry (18 to 39, 40 to 64, ≥ 65 years), race (asian, black, white, other), ethnic group (Hispanic or Latino, Not Hispanic or Latino), site location (Site XXX, Site XXX, Other Sites), use of antiviral therapies or immunomodulatory drugs through the study (Yes, No), previous COVID-19 vaccination status (Fully vaccinated, Non-fully vaccinated, No vaccinated), anti-SARS-CoV-2 IgG at Day 1 (Non-positive, Positive), pre-randomisation dexamethasone (Yes, No), total duration of corticoid therapy (< 9 days, [9 – 11] days, > 11 days), total cumulative dose of corticoid therapy (dexamethasone or equivalent) (≤ 60 mg, > 60 mg), SARS-CoV-2 viral load (log10 copies/mL) at Day 1 before study drug administration (< 4, [4 - 7], > 7), time between onset date of COVID-19 symptoms and initiation of study treatment (≤ 5 days, 6 - 10 days, > 10 days), body mass index (kg/m2) at Screening (< 30, ≥ 30), hypertension at Screening (Yes, No), myocardial infarction (Yes, No), congestive heart failure (Yes, No), peripheral vascular disease (Yes, No), cerebrovascular disease (Yes, No), dementia (Yes, No), chronic obstructive pulmonary disease (Yes, No), connective tissue disease (Yes, No), peptic ulcer disease (Yes, No), liver disease (None, Mild, Moderate or Severe), diabetes mellitus (None or diet controlled, Uncomplicated, End-organ damage), hemiplegia (Yes, No), moderate or severe chronic kidney disease (Yes, No), solid tumor (None, Localized, Metastatic), leukemia (Yes, No), lymphoma (Yes, No), AIDS (Yes, No), ISARIC-4C mortality score (Low (0 - 3), Intermediate (4 - 8), High (9 - 14), Very high (≥ 15)), ISARIC-4C deterioration probability (≤ 25, (25 - 50], > 50), LDH at Baseline (≤ ULN, > ULN), CRP (mg/L) at Baseline (≤ 100, > 100), D-dimer at Baseline (≤ ULN, > ULN), ferritin at Baseline (≤ ULN, > ULN), creatinine at Baseline (≤ ULN, > ULN), IL-6 at Baseline (≤ Median, > Median), IL-10 at Baseline (≤ Median, > Median), lymphocytes count decreased at Baseline (Grade 0, Grade ≥ 1), neutrophils/lymphocytes ratio at Baseline (< 6, ≥ 6) and SARS-CoV-2 variant (Alpha, Beta, Gamma, Delta, Eta, Iota, Kappa, Lambda, Mu, any potential new variant) as covariates. Those covariates with more than 10% of missing values are omitted. A stepwise selection model is used, with significant level equal to 0.2 and 0.05, to enter into the model and to remain in the model, respectively.

*Programming notes (not part of the table):*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Omit those covariates with more than 10% of missing values from the multivariate analysis.*
- *Force to include the treatment arm in addition to the significant covariates.*

**Table 14.2.4.3.1 Time to Sustained Withdrawal of Oxygen Supplementation - Control Arm with Antiviral (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm with Antiviral [a] (N=XXX) |
|---|---|---|---|
| Patients who Reported Sustained Withdrawal of Oxygen Supplementation, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Sustained Withdrawal of Oxygen Supplementation (days) 95% CI [b] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [c] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [d,e] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Those patients randomised to the control arm receiving the antiviral control arm (i.e., remdesivir or favipiravir).
[b] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[c] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

**Table 14.2.4.3.2 Time to Sustained Withdrawal of Oxygen Supplementation - Control Arm without Antiviral (Intent-To-Treat Population)**

| Variable | Plitidepsin 2.5mg (N=XXX) | Plitidepsin 1.5mg (N=XXX) | Control Arm without Antiviral [a] (N=XXX) |
|---|---|---|---|
| Patients who Reported Sustained Withdrawal of Oxygen Supplementation, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Censored Patients, n (%) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Time-to Sustained Withdrawal of Oxygen Supplementation (days) 95% CI [b] | | | |
| 25th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Median | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| 75th percentile | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| Mean (SE) | xx.x (xx.x) | xx.x (xx.x) | xx.x (xx.x) |
| Stratified Log-Rank Test | | | |
| 2-sided p-value [c] | x.xxx | x.xxx | |
| Supportive Analysis - Stratified Cox Regression Model | | | |
| Hazard Ratio [d,e] | x.xxx | x.xxx | |
| 95% CI for Hazard Ratio [d,e] | x.xxx – x.xxx | x.xxx – x.xxx | |
| 2-sided p-value [d] | x.xxx | x.xxx | |

N = number of patients in analysis set. % = percentages are calculated based on N as the denominator.
CI = Confidence interval; SE = Standard Error.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

[a] Those patients randomised to the control arm without receiving the antiviral control arm (i.e., remdesivir or favipiravir).
[b] Calculated using the Kaplan-Meier estimator. CIs derived based on Brookmeyer-Crowley method and using a log log transformation.
[c] 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates.
[d] Hazard Ratio, 95% CI and 2-sided p-values calculated using a stratified Cox proportional-hazards regression model, including the fixed effect of the treatment group and levels of the randomisation stratification factors, ie, geographical region (Europe vs. Rest of the World), Charlson Comorbidity Index (0-1 vs. >1) and pre-baseline Barthel index (≥90 versus <90) as derived using the eCRF data as covariates. Hazard Ratio > 1 favours a Plitidepsin arm to be associated with a shorter time to sustained withdrawal of oxygen supplementation than Control Arm.
[e] Statistics calculated relative to Control Arm.
Reference: Listing 16.2.6.5

*Programming notes (not part of the table):*

- *Table template TEF011A.*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *If 25th percentile, median or 75th percentile is not reached, present as "NR".*

## 3.11 Exposure

**Table 14.3.1.1 Summary of Exposure (As Treated Population)**

| Exposure | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Control Arm (N=XXX) | | |
|---|---|---|---|---|---|---|---|
| Statistic | Dexamethasone | Plitidepsin | Dexamethasone | Plitidepsin | Dexamethasone | Remdesivir | Favipiravir |
| Number of Patients with at least one Infusion/Dose Administered, n | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Duration of Exposure (days) [a] | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx |
| Days with Doses Administered | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx |
| Days with Doses Administered, n (%) | | | | | | | |
| 1 day | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 2 days | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 3 days | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 4 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 5 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 6 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 7 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 8 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 9 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 10 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| >10 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on the number of patients with at least one infusion/dose administered as the denominator.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum; NA= Not Applicable.
[a] Duration is defined as (last dose date - first dose date + 1).
Reference: Listing 16.2.5.1 and 16.2.5.2

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *The ">10 infusions/doses" category should only be presented if there are any cases in any treatment group.*

**Table 14.3.1.1 Summary of Exposure (As Treated population)**

| Exposure | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Control Arm (N=XXX) | | |
|---|---|---|---|---|---|---|---|
| **Statistic** | **Dexamethasone** | **Plitidepsin** | **Dexamethasone** | **Plitidepsin** | **Dexamethasone** | **Remdesivir** | **Favipiravir** |
| Days where Total Amount was Administered | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx |
| Days where Total Amount was Administered, n (%) | | | | | | | |
| 0 day | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 1 day | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 2 days | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 3 days | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 4 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 5 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 6 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 7 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 8 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 9 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 10 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| >10 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on the number of patients with at least one infusion/dose administered as the denominator.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum; NA= Not Applicable.
[a] Duration is defined as (last dose date - first dose date + 1).
Reference: Listing 16.2.5.1 and 16.2.5.2

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *The ">10 infusions/doses" category should only be presented if there are any cases in any treatment group.*

**Table 14.3.1.1 Summary of Exposure (As Treated population)**

| Exposure | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Control Arm (N=XXX) | | |
|---|---|---|---|---|---|---|---|
| **Statistic** | **Dexamethasone** | **Plitidepsin** | **Dexamethasone** | **Plitidepsin** | **Dexamethasone** | **Remdesivir** | **Favipiravir** |
| Days where Total Amount was NOT Administered | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) | xx.x (xx.xx) |
| Median | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x | xx.x |
| Q1, Q3 | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| Min, Max | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx | xx, xx |
| Days where Total Amount was NOT Administered, n (%) | | | | | | | |
| 0 day | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 1 day | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 2 days | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 3 days | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 4 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 5 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| 6 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 7 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 8 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 9 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| 10 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |
| >10 days | xxx (xxx.x) | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on the number of patients with at least one infusion/dose administered as the denominator.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum; NA= Not Applicable.
[a] Duration is defined as (last dose date - first dose date + 1).
Reference: Listing 16.2.5.1 and 16.2.5.2

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *The ">10 infusions/doses" category should only be presented if there are any cases in any treatment group.*

**Table 14.3.1.1 Summary of Exposure (As Treated population)**

| Exposure | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Control Arm (N=XXX) | | |
|---|---|---|---|---|---|---|---|
| Statistic | Dexamethasone | Plitidepsin | Dexamethasone | Plitidepsin | Dexamethasone | Remdesivir | Favipiravir |
| Infusions Interrupted | | | | | | | |
| n | NA | xxx | NA | xxx | NA | NA | NA |
| Mean (SD) | | xx.x (xx.xx) | | xx.x (xx.xx) | | | |
| Median | | xx.x | | xx.x | | | |
| Q1, Q3 | | xx.x, xx.x | | xx.x, xx.x | | | |
| Min, Max | | xx, xx | | xx, xx | | | |
| Infusions Interrupted, n (%) | | | | | | | |
| 0 infusion | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA | NA |
| 1 infusion | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA | NA |
| 2 infusions | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA | NA |
| 3 infusions | NA | xxx (xxx.x) | NA | xxx (xxx.x) | NA | NA | NA |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on the number of patients with at least one infusion/dose administered as the denominator.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum; NA= Not Applicable.
[a] Duration is defined as (last dose date - first dose date + 1).
Reference: Listing 16.2.5.1 and 16.2.5.2

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

## 3.12 Adverse Events

**Table 14.3.1.2 Summary of Treatment-Emergent Adverse Events (TEAEs) (As Treated Population)**

| Adverse Events Category<br>Adverse Events Type | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Plitidepsin Total<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Any TEAE | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 1 severity | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 2 severity | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 3 severity | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 4 severity | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 5 severity | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade >= 3 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to discontinuation of any study drug | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Any treatment-related TEAE to any study drug [a] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade >= 3 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to discontinuation of any study drug | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Any treatment-related TEAE to plitidepsin [a] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | NA |
| Grade >= 3 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | NA |
| Leading to discontinuation of any study drug | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | NA |
| Leading to death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | NA |
| Any treatment-related TEAE to dexamethasone [a] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade >= 3 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to discontinuation of any study drug | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] A treatment-related TEAE to any study drug, plitidepsin, dexamethasone or to the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir), is an TEAE considered by the investigator as related to the corresponding study drug or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE001.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.2 Summary of Treatment-Emergent Adverse Events (TEAEs) (As Treated population)**

| Adverse Events Category<br>Adverse Events Type | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Plitidepsin Total<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| Any treatment-related TEAE to the antiviral control arm [a] | NA | NA | NA | xxx (xxx.x) |
| Grade >= 3 | NA | NA | NA | xxx (xxx.x) |
| Leading to discontinuation of any study drug | NA | NA | NA | xxx (xxx.x) |
| Leading to death | NA | NA | NA | xxx (xxx.x) |
| Any serious TEAE | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade >= 3 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to discontinuation of any study drug | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Any serious treatment-related TEAE to any study drug [a] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade >= 3 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Any serious treatment-related TEAE to plitidepsin [a] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | NA |
| Any serious treatment-related TEAE to dexamethasone [a] | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Any serious treatment-related TEAE to the antiviral control arm [a] | NA | NA | NA | xxx (xxx.x) |
| Any TEAE of special interest | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade >= 3 | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to discontinuation of any study drug | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Leading to death | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] A treatment-related TEAE to plitidepsin, dexamethasone or to the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir), is an TEAE considered by the investigator as related to the corresponding study drug or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE001.*

- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.3.1 TEAEs by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one TEAE | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *The number and percentage of patients first row of this table should match the same count in table template TAE001.*

**Table 14.3.1.3.2 TEAEs by Grouped Preferred Term (As Treated Population)**

| Grouped Preferred Term | Plitidepsin 2.5mg (N=XXX) n (%) E | Plitidepsin 1.5mg (N=XXX) n (%) E | Plitidepsin Total (N=XXX) n (%) E | Control Arm (N=XXX) n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one TEAE | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE003.*
- *Sort by descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.3.3 TEAEs by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one TEAE | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 4 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 5 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade >= 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*

**Table 14.3.1.3.4 TEAEs Leading to Discontinuation of Any Study Drug by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one TEAE leading to discontinuation of any study drug | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.3.5 TEAEs Leading to Death by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one TEAE leading to death | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
MedDRA version &meddra.
Reference: Listing 16.2.7.3

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.4.1 Treatment-related TEAEs to any Study Drug (Plitidepsin, Dexamethasone or Antiviral Control Arm) by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to any study drug [b] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to any study drug is a TEAE considered by the investigator as related to plitidepsin, dexamethasone, the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir) or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.4.2 Treatment-related TEAEs to any Study Drug (Plitidepsin, Dexamethasone or Antiviral Control Arm) by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to any study drug [c] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 4 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 5 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade >= 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
[c] A treatment-related TEAE to any study drug is a TEAE considered by the investigator as related to plitidepsin, dexamethasone, the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir) or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*

**Table 14.3.1.4.3 Treatment-related TEAEs to Plitidepsin by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to plitidepsin [b] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to plitidepsin is a TEAE considered by the investigator as related to plitidepsin or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.4.4 Treatment-related TEAEs to Plitidepsin by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to plitidepsin [c] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grade 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grade 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grade 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grade 4 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grade 5 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grade >= 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
[c] A treatment-related TEAE to plitidepsin is a TEAE considered by the investigator as related to plitidepsin or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*

**Table 14.3.1.4.5 Treatment-related TEAEs to Dexamethasone by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to dexamethasone [b] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to dexamethasone is a TEAE considered by the investigator as related to dexamethasone or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.4.6 Treatment-related TEAEs to Dexamethasone by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to dexamethasone [c] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 4 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 5 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade >= 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
[c] A treatment-related TEAE to dexamethasone is a TEAE considered by the investigator as related to dexamethasone or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.4.7 Treatment-related TEAEs to the Antiviral Control Arm by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg (N=XXX)<br>n (%) E | Plitidepsin 1.5mg (N=XXX)<br>n (%) E | Plitidepsin Total (N=XXX)<br>n (%) E | Control Arm (N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to the Antiviral Control Arm [b] | NA | NA | NA | xxx (xxx.x) xxx |
| System Organ Class 1 | NA | NA | NA | xxx (xxx.x) xxx |
| Grouped Preferred Term A | NA | NA | NA | xxx (xxx.x) xxx |
| Grouped Preferred Term B | NA | NA | NA | xxx (xxx.x) xxx |
| System Organ Class 2 | NA | NA | NA | xxx (xxx.x) xxx |
| Grouped Preferred Term C | NA | NA | NA | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to the antiviral control arm is a TEAE considered by the investigator as related to the antiviral control arm (i.e., remdesivir or favipiravir) or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.1.4.8 Treatment-related TEAEs to the Antiviral Control Arm by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Treatment-related TEAEs to the Antiviral Control Arm [c] | NA | NA | NA | xxx (xxx.x) xxx |
| System Organ Class 1 | NA | NA | NA | xxx (xxx.x) xxx |
| Grouped Preferred Term A | NA | NA | NA | xxx (xxx.x) xxx |
| Grade 1 | NA | NA | NA | xxx (xxx.x) xxx |
| Grade 2 | NA | NA | NA | xxx (xxx.x) xxx |
| Grade 3 | NA | NA | NA | xxx (xxx.x) xxx |
| Grade 4 | NA | NA | NA | xxx (xxx.x) xxx |
| Grade 5 | NA | NA | NA | xxx (xxx.x) xxx |
| Grade >= 3 | NA | NA | NA | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
[c] A treatment-related TEAE to the antiviral control arm is a TEAE considered by the investigator as related to the antiviral control arm (i.e., remdesivir or favipiravir) or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*

**Table 14.3.2.1.1 Listing of Deaths (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Treatment Start Date Time (Day)/ Stop Date Time (Day) [b]/ Duration (Days) | Death Date (Day) [b] | Cause of Death | Relationship in any way to the Study Disease COVID-19 | Fatal AE (Grouped Preferred Term) |
|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY HH:MM (XX)/ DDMMMYYYY HH:MM (XX)/ XX | DDMMMYYYY (XX) | Adverse Event or Other: xxxxxxxxxxxx | Yes or No | xxxxxxxxxxxx |
| 123-456789 | 45/M/W | 19JUL2018 (1)/ 24JUL2018 (6)/ 6 | 24JUL2018 (6) | Adverse Event | No | Arrhythmia NOS |
| etc. | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE003.*
- *Order by Site ID - Patient ID.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.1.2 Summary of Deaths (As Treated Population)**

| | Plitidepsin 2.5mg (N=XXX) n (%) | Plitidepsin 1.5mg (N=XXX) n (%) | Plitidepsin Total (N=XXX) n (%) | Control Arm (N=XXX) n (%) |
|---|---|---|---|---|
| Number of Deaths | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Cause of Death | | | | |
| Adverse Event | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Other | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
Reference: Table 14.3.2.1.1

*Programming notes (not part of the table):*

- *Table template TAE008.*
- *Sort reasons for Death as specified in the eCRF.*

**Table 14.3.2.2.1 Listing of Serious Adverse Events (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class/ Grouped Preferred Term/ Verbatim | Start Date (Day)/ Stop Date (Day) [b]/ Duration (Days) or Ongoing | TEAE [c] | Severity/ Seriousness criteria | Relationship to Trial Medication | Action taken to Plitidepsin/ Dexamethasone/ Antiviral Control Arm [d] | Outcome |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX | | Grade X/<br>xxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | xxxxxxxxxxxx |
| 123-456789 | 45/M/W | Infections and infestations/<br>Pharyngitis/<br>Acute Pharyngitis | 19JUL2018 (56)/<br>24JUL2018 (61)/<br>6 | * | Grade 2/<br>Requires Or Prolongs Hospitalization | Yes - Related to Dexamethasone | Not Applicable/<br>Not changed/<br>Omitted | Recovered/<br>Resolved |
| | | Musculoskeletal and connective tissue disorders/<br>Periarthritis/<br>Shoulder Periarthritis(Both) | 14AUG2018 (82)/<br>ONGOING | * | Grade 3/<br>Life Threatening | No - Study disease | Not Applicable/<br>Not changed/<br>Unknown | Recovering/<br>Resolving |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] TEAE=Treatment Emergent Adverse Event. TEAEs are flagged with *.
[d] Antiviral control arm is the regulatory-approved antiviral for those patients randomised to the control arm, i.e., remdesivir or favipiravir.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE002.*
- *Order by Site ID - Patient ID and AE No.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.3.1 Serious TEAEs by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Serious TEAE | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.3.2 Serious TEAEs by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Serious TEAE | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 4 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 5 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade >= 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*

**Table 14.3.2.3.3 Serious Treatment-related TEAEs to any Study Drug (Plitidepsin, Dexamethasone or Antiviral Control Arm) by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Serious Treatment-related TEAEs to any study drug [b] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to any study drug is a TEAE considered by the investigator as related to plitidepsin, dexamethasone, the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir) or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.3.4 Serious Treatment-related TEAEs to any Study Drug (Plitidepsin, dexamethasone or Antiviral Control Arm) by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Serious Treatment-related TEAEs to any study drug [c] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 4 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 5 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
[c] A treatment-related TEAE to any study drug is a TEAE considered by the investigator as related to plitidepsin, dexamethasone, the antiviral control arm, ie, the regulatory-approved antiviral for those patients randomised to the control arm (remdesivir or favipiravir) or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*

**Table 14.3.2.4.1 Serious Treatment-related TEAEs to Plitidepsin by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Serious Treatment-related TEAEs to plitidepsin [b] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | NA |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to plitidepsin is an TEAE considered by the investigator as related to plitidepsin or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.4.2 Serious Treatment-related TEAEs to Dexamethasone by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Serious Treatment-related TEAEs to dexamethasone [b] | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to dexamethasone is an TEAE considered by the investigator as related to dexamethasone or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.4.3 Serious Treatment-related TEAEs to the Antiviral Control Arm by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg (N=XXX)<br>n (%) E | Plitidepsin 1.5mg (N=XXX)<br>n (%) E | Plitidepsin Total (N=XXX)<br>n (%) E | Control Arm (N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one Serious Treatment-related TEAEs to the Antiviral Control Arm [b] | NA | NA | NA | xxx (xxx.x) xxx |
| System Organ Class 1 | NA | NA | NA | xxx (xxx.x) xxx |
| Grouped Preferred Term A | NA | NA | NA | xxx (xxx.x) xxx |
| Grouped Preferred Term B | NA | NA | NA | xxx (xxx.x) xxx |
| System Organ Class 2 | NA | NA | NA | xxx (xxx.x) xxx |
| Grouped Preferred Term C | NA | NA | NA | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event; NA= Not Applicable.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] A treatment-related TEAE to the antiviral control arm is an TEAE considered by the investigator as related to the antiviral control arm (i.e., remdesivir or favipiravir) or with unknown/missing relationship to trial medication.
MedDRA version &meddra.
Reference: Listing 16.2.7.1

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.5 Listing of Adverse Events Leading to Discontinuation of any Study Drug (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class/ Grouped Preferred Term/ Verbatim | Start Date (Day)/ Stop Date (Day) [b]/ Duration (Days) or Ongoing | TEAE [c] | Severity/ Seriousness criteria | Relationship to Trial Medication | Action taken to Plitidepsin/ Dexamethasone/ Antiviral Control Arm [d] | Outcome |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX | | Grade X/<br>xxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | xxxxxxxxxxxx |
| 123-456789 | 45/M/W | Infections and infestations/<br>Pharyngitis/<br>Acute Pharyngitis | 19JUL2018 (56)/<br>24JUL2018 (61)/<br>6 | * | Grade 2/<br>Requires Or Prolongs Hospitalization | Yes - Related to Antiviral Control Arm | Not Applicable/<br>Treatment Withdrawn/<br>Not changed | Recovered/<br>Resolved |
| | | Musculoskeletal and connective tissue disorders/<br>Periarthritis/<br>Shoulder Periarthritis(Both) | 14AUG2018 (82)/<br>ONGOING | * | Grade 3/<br>Life Threatening | Yes - Related to Dexamethasone | Not Applicable/<br>Not changed/<br>Treatment Withdrawn | Recovering/<br>Resolving |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] TEAE=Treatment Emergent Adverse Event. TEAEs are flagged with *.
[d] Antiviral control arm is the regulatory-approved antiviral for those patients randomised to the control arm, i.e., remdesivir or favipiravir.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE002.*
- *Order by Site ID - Patient ID and AE No.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.6.1 TEAEs of special interest by System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one TEAE of special interest | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term B | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term C | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
MedDRA version &meddra.
Reference: Listing 16.2.7.4

*Programming notes (not part of the table):*

- *Table template TAE002.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Table 14.3.2.6.2 TEAEs of special interest by Maximum Severity, System Organ Class and Grouped Preferred Term (As Treated Population)**

| System Organ Class<br>Grouped Preferred Term [a]<br>Maximum Severity [b] | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) E | Plitidepsin Total<br>(N=XXX)<br>n (%) E | Control Arm<br>(N=XXX)<br>n (%) E |
|---|---|---|---|---|
| Number of Patients with at least one TEAE of special interest | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| System Organ Class 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grouped Preferred Term A | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 1 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 2 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 4 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade 5 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| Grade >= 3 | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx | xxx (xxx.x) xxx |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on N as the denominator; E = number of events.
TEAE = Treatment Emergent Adverse Event.
Note: TEAEs are events with start date on or after the date of first dose of any study drug or events with start date prior to the date of first dose of any study drug whose severity worsens on or after the date of first dose of any study drug. If the event started on the date of first dose of the first study drug administration however it is ticked as the event started prior to first study drug administration on Day 1 in the eCRF, it is not considered as a TEAE.
Adverse events were assigned severity grade using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
[a] Within a system organ class, patients may have reported more than one grouped preferred term. Patients are counted once for each grouped preferred term and each system organ class.
[b] Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT.
MedDRA version &meddra.
Reference: Listing 16.2.7.4

*Programming notes (not part of the table):*

- *Table template TAE005.*
- *Sort alphabetically by system organ class and descending grouped preferred term in the total column. Where grouped preferred terms tie these should be sorted alphabetically.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *If a patient experienced more than one AE within the same SOC and PT, the AE with the maximum intensity should be counted for that SOC and PT.*

## 3.13 Laboratory Data

**Table 14.3.4.1 Summary of Laboratory Results - Haematology (As Treated Population)**

**Parameter (unit)**

| | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Plitidepsin Total (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|---|---|
| **Visit** / **Statistic** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** |
| Baseline | | | | | | | | |
| n | xxx | | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| <<Day X>> | | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
Reference: Listing 16.2.8.1.1

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *Parameters are: Red Blood Cell Count, Haemoglobin, Haematocrit, White Blood Cell Count, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, and Platelet Count.*
- *Visits: Day 2, Day 3, Day 4, Day 8, and Day 31.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.3.4.2 Summary of Laboratory Results - Serum Chemistry (As Treated Population)**

**Parameter (unit)**

| | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Plitidepsin Total (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|---|---|
| **Visit** / **Statistic** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** |
| Baseline | | | | | | | | |
| n | xxx | | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| <<Day X>> | | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
Reference: Listing 16.2.8.1.2

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *Parameters are: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, Gamma-Glutamyltransferase (GGT), Total Bilirubin, Direct Bilirubin, Glucose (fasting), Sodium, Potassium, Calcium (adjusted), Magnesium, Creatinine, Calculated Creatinine Clearance (Cockcroft Gault equation), Albumin, Creatine Phosphokinase (CPK), Troponin T, N-terminal pro b-type natriuretic peptide (NT-pro-BNP), Blood Urea Nitrogen, Amylase, Lipase, and Procalcitonin.*
- *Visits: Day 2, Day 3, Day 4, Day 8, and Day 31.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.3.4.3 Summary of Laboratory Results - Coagulation (As Treated Population)**

**D-dimer (unit)**

| | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Plitidepsin Total (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|---|---|
| **Visit** / **Statistic** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** |
| Baseline | | | | | | | | |
| n | xxx | | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| <<Day X>> | | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
Reference: Listing 16.2.8.1.4

*Programming notes (not part of the table):*

- *Table template TLB004B.*
- *Visits: Day 2, Day 3, Day 4, Day 8, and Day 31.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.3.4.4 Summary of Laboratory Results - Haematology - Worst Grade NCI-CTCAE Toxicity Shifts from Baseline (As Treated Population)**

**Parameter – xxxx**

| Treatment Group<br>Baseline CTCAE Grade | CTCAE Worst Grade Post-Baseline value | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade>=1 | Grade>=3 | Missing | Total [a] |
| Plitidepsin 2.5mg (N=XXX) | | | | | | | | | |
| Grade 0, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 1, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 2, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 3, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 4, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Missing, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade>=1, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade>=3, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Total, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Plitidepsin 1.5mg (N=XXX) | | | | | | | | | |
| etc. | | | | | | | | | |
| Control Arm (N=XXX) | | | | | | | | | |
| etc. | | | | | | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on the Total number per row as the denominator.
[a] For Total column, percentages are calculated based on total number of patients with non-missing values at Baseline or Post-Baseline as the denominator.
Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
Worst grade post-Baseline value is the highest post-Baseline grade recorded through the study.
'Low' relates to NCI-CTC grades for low results, 'High' relates to NCI-CTC grades for high results.
Grades were assigned using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
Reference: Listing 16.2.8.1.1

*Programming notes (not part of the table):*

- *Table template TLB006.*
- *Parameters are: Haemoglobin - Low, Haemoglobin - High, White Blood Cell Count - Low, White Blood Cell Count - High, Neutrophils - Low, Eosinophils - High, Lymphocytes - Low, Lymphocytes - High, and Platelet Count - Low.*

**Table 14.3.4.5 Summary of Laboratory Results - Serum Chemistry - Worst Grade NCI-CTCAE Toxicity Shifts from Baseline (As Treated Population)**

**Parameter – xxxx**

| Treatment Group<br>Baseline CTCAE Grade | CTCAE Worst Grade Post-Baseline value | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Grade 0** | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade>=1** | **Grade>=3** | **Missing** | **Total [a]** |
| Plitidepsin 2.5mg (N=XXX) | | | | | | | | | |
| Grade 0, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 1, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 2, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 3, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade 4, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Missing, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade>=1, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Grade>=3, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Total, n (%) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) | xxx (xxx.x) |
| Plitidepsin 1.5mg (N=XXX) | | | | | | | | | |
| etc. | | | | | | | | | |
| Control Arm (N=XXX) | | | | | | | | | |
| etc. | | | | | | | | | |

N = number of patients in analysis set; n = number of patients with data available; % = percentages are calculated based on the Total number per row as the denominator.
[a] For Total column, percentages are calculated based on total number of patients with non-missing values at Baseline or Post-Baseline as the denominator.
Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
Worst grade post-Baseline value is the highest post-Baseline grade recorded through the study.
'Low' relates to NCI-CTC grades for low results, 'High' relates to NCI-CTC grades for high results.
Grades were assigned using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
Reference: Listing 16.2.8.1.2

*Programming notes (not part of the table):*

- *Table template TLB006.*
- *Parameters are: Alanine aminotransferase (ALT) - High, Aspartate aminotransferase (AST) - High, Alkaline phosphatase - High, Gamma-Glutamyltransferase (GGT) - High, Lactate dehydrogenase (LDH) - High, Total Bilirubin - High, Glucose (fasting) - Low, Sodium - Low, Sodium - High, Potassium - Low, Potassium - High, Calcium - Low, Calcium - High, Magnesium - Low, Magnesium - High, Creatinine - High, Albumin - Low, Creatine Phosphokinase (CPK) - High, Troponin T - High, Amylase - High, and Lipase - High.*

## 3.14 Vital Signs

**Table 14.3.5.1 Summary of Vital Signs and Oxygen Saturation - Change from Baseline (As Treated Population)**

**Parameter (unit)**

| | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Plitidepsin Total (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|---|---|
| **Visit Statistic** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** |
| Baseline | | | | | | | | |
| n | xxx | | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| Day 2 – Pre-Infusion | | | | | | | | |
| N | xxx | xxx | xxx | xxx | xxx | xxx | NA | NA |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | | |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | | |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | | |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | | |
| Day 2 | | | | | | | | |
| n | NA | NA | NA | NA | NA | NA | xxx | xxx |
| Mean (SD) | | | | | | | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | | | | | | | xx.xx | xx.xx |
| Q1, Q3 | | | | | | | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | | | | | | | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum; NA= Not Applicable.
Notes: The baseline value is defined as last scheduled or unscheduled non-missing value collected prior to the first dose of the first study drug administration.
Reference: Listing 16.2.8.2.1

*Programming notes (not part of the table):*

- *Table template TVS002B.*
- *Parameters are: Systolic Blood Pressure (mmHg); Diastolic Blood Pressure (mmHg), Pulse rate (beats/min); Temperature (°C); Respiration Rate (breaths/min) and Oxygen Saturation at Room Air (%).*
- *Visits: Day 2 – Pre-Infusion, Day 2, Day 3 – Pre-Infusion, Day 3, Day 4, Day 5, Day 6, Day 7, Day 8, and Day 31.*

- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.3.5.2 Summary of Vital Signs and Oxygen Saturation - Change during Plitidepsin Infusion (As Treated Population)**

| Parameter (unit) | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Plitidepsin Total (N=XXX) | |
|---|---|---|---|---|---|---|
| Visit<br>Timepoint<br>Statistic | Value at Timepoint | Change from the Start of the Infusion | Value at Timepoint | Change from the Start the of Infusion | Value at Timepoint | Change from the Start the of Infusion |
| <<Day X>> | | | | | | |
| Before the Start of the Plitidepsin Infusion | | | | | | |
| n | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| Immediately at the End of the Plitidepsin Infusion | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation; Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Notes: The change from the start to the end of the plitidepsin infusion = immediately at end of the plitidepsin infusion value - before the start of the plitidepsin infusion value.
Reference: Listing 16.2.8.2.1

*Programming notes (not part of the table):*

- *Table template TVS002B.*
- *Parameters are: Systolic Blood Pressure (mmHg); Diastolic Blood Pressure (mmHg), Pulse rate (beats/min); Temperature (°C); Respiration Rate (breaths/min) and Oxygen Saturation at Room Air (%).*
- *Visits: Day 1, Day 2 and Day 3.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

## 3.15 Electrocardiograms (ECGs)

**Table 14.3.6.1 Summary of 12-Lead Electrocardiogram (ECG) Parameters - Change from Baseline (As Treated Population)**

**Parameter (unit)**

| | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Plitidepsin Total (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|---|---|
| **Visit** / **Statistic** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** | **Value at Visit** | **Change from Baseline** |
| Baseline | | | | | | | | |
| n | xxx | | xxx | | xxx | | xxx | |
| Mean (SD) | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | | xx.xx (xx.xxx) | |
| Median | xx.xx | | xx.xx | | xx.xx | | xx.xx | |
| Q1, Q3 | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | | xx.xx, xx.xx | |
| Min, Max | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | | xx.x, xx.x | |
| <<Day X>> | | | | | | | | |
| n | xxx | xxx | xxx | xxx | xxx | xxx | xxx | xxx |
| Mean (SD) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) | xx.xx (xx.xxx) |
| Median | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx | xx.xx |
| Q1, Q3 | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx | xx.xx, xx.xx |
| Min, Max | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x | xx.x, xx.x |
| etc. | | | | | | | | |

N = number of patients in analysis set; n = number of patients with data available.
SD = Standard deviation;Q1 = 25th percentile; Q3 = 75th percentile; Min = Minimum; Max = Maximum.
Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value collected prior to the first dose of the first study drug administration.
Reference: Listing 16.2.8.3.2

*Programming notes (not part of the table):*

- *Table template TEG002B.*
- *Parameter is: Average QTcF interval (msec).*
- *Visits: Day 1 - Post-infusion, Day 3 - Post-infusion and Day 31.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*

**Table 14.3.6.2 Potentially Clinically Important (PCI) Electrocardiogram (ECG) Results (As Treated Population)**

| Visit<br>Parameter<br>PCI Criterion | Plitidepsin 2.5mg<br>(N=XXX)<br>n (%) | Plitidepsin 1.5mg<br>(N=XXX)<br>n (%) | Plitidepsin Total<br>(N=XXX)<br>n (%) | Control Arm<br>(N=XXX)<br>n (%) |
|---|---|---|---|---|
| <<Day X>> | | | | |
| Patients at <<Day X>>, n1 | xxx | xxx | xxx | xxx |
| Average QTcF Interval | | | | |
| >500 msec | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Change from baseline > 30 msec | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; n1 = number of patients with data available at visit; % = percentages are calculated based on n1 as the denominator;
QTcF = QT correction as calculated by Fridericia's formula.
Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value collected prior to the first dose of the first study drug administration.
Reference: Listing 16.2.8.3.2

*Programming notes (not part of the table):*

- *Table template TEG005A.*
- *Visits: Day 1 - Post-infusion, Day 3 - Post-infusion and Day 31.*
- *Follow first footnote for calculation of percentages.*

## 3.16 Functional Status - Barthel Index

**Table 14.3.7.1 Functional Status - Barthel Index (As Treated Population)**

| Visit<br>Barthel Index Score | Plitidepsin 2.5mg (N=XXX)<br>n (%) | Plitidepsin 1.5mg (N=XXX)<br>n (%) | Plitidepsin Total (N=XXX)<br>n (%) | Control Arm (N=XXX)<br>n (%) |
|---|---|---|---|---|
| Previous Month to COVID-19 Infection | | | | |
| Patients with Previous Month to COVID-19 Infection assessment, n1 | xxx | xxx | xxx | xxx |
| 100% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 90% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 85% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 80% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| <80% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| Screening | | | | |
| 100% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 90% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 85% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 80% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| <80% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| << Visit>> | | | | |
| Patients at << Visit>>, n1 | xxx | xxx | xxx | xxx |
| 100% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 95% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 90% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 85% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| 80% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| <80% | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| etc. | | | | |

N = number of patients in analysis set; n = number of patients with data available; n1 = number of patients with data available at visit; % = percentages are calculated based on N for Screening or otherwise, on n1 as the denominator.
Reference: Listing 16.2.6.2

*Programming notes (not part of the table):*

- *Table template TEG005A.*
- *Visits: Previous Month to COVID-19 Infection, Screening, Day 8, Day 15, Day 31 and At Discharge from Hospital.*
- *Follow first footnote for calculation of percentages.*

## 3.17 Safety subgroup analyses

**Table 14.3.8.1 Summary of TEAEs and Clinically Relevant Laboratory Tests - Worst Grade Post-Baseline - Subgroup Analysis (As Treated Population)**

**<<Subgroup>>**

| | Plitidepsin 2.5mg (N=XXX) | | Plitidepsin 1.5mg (N=XXX) | | Plitidepsin Total (N=XXX) | | Control Arm (N=XXX) | |
|---|---|---|---|---|---|---|---|---|
| **Laboratory Abnormality/ TEAE** | **Grade >=1 or (>=ULN if not NCI-CTCAE grade) n (%)** | **Grade >=3 n (%)** | **Grade >=1 or (>=ULN if not NCI-CTCAE grade) n (%)** | **Grade >=3 n (%)** | **Grade >=1 or (>=ULN if not NCI-CTCAE grade) n (%)** | **Grade >=3 n (%)** | **Grade >=1 or (>=ULN if not NCI-CTCAE grade) n (%)** | **Grade >=3 n (%)** |
| CTCAE: Anemia | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: Platelet count decreased | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: Neutrophil count decreased | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: AP increased | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: Blood bilirubin increased | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: AST increased | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: ALT increased | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: CPK increased | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| CTCAE: LDH increased | xxx (xx.x) | NA | xxx (xx.x) | NA | xxx (xx.x) | NA | xxx (xx.x) | NA |
| Ferritin | xxx (xx.x) | NA | xxx (xx.x) | NA | xxx (xx.x) | NA | xxx (xx.x) | NA |
| D-dimer | xxx (xx.x) | NA | xxx (xx.x) | NA | xxx (xx.x) | NA | xxx (xx.x) | NA |
| TEAE: Nausea | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| TEAE: Vomiting | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| TEAE: Fatigue | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |
| TEAE: xxxxxxxxxxx [a] | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) | xxx (xx.x) |

N = number of patients in analysis set within the subgroup; n = number of patients with data available; % = percentages are calculated based on N as the denominator.
[a] Grouped PT term presented in more than 5% of the patients within any treatment group.
Reference: Listing 16.2.7.1, 16.2.8.1.1, 16.2.8.1.2 and 16.2.8.1.4

*Programming notes (not part of the table):*

- *Use the PT = Nausea for TEAE: Nausea; the PT = Vomiting for TEAE: Vomiting and the PT = Fatigue for TEAE: Fatigue.*
- *Add the grouped PT terms presented in more than 5% of the patients within any treatment group.*
- *Subgroups are:*
  - *Sex: female or male*
  - *Age at study entry: 18 to 39, 40 to 64, ≥ 65 years*
  - *Race: Asian, black, white, or other*
  - *Ethnic group: 'Hispanic or Latino' or 'Not Hispanic or Latino'*

- *Site location: Site XXX, Site XXX or Other Sites*
- *Previous COVID-19 vaccination status: 'Fully vaccinated', 'Non-fully vaccinated' or 'No vaccinated'*
- *SARS CoV 2 viral load (log10 copies/mL) at Day 1 before study drug administration: < 4, [4-7], > 7*
- *Time between onset date of COVID-19 symptoms and initiation of study treatment: ≤ 5 days, 6 - 10 days, > 10 days*
- *Charlson Comorbidity Index (as derived using the eCRF data): 0 - 1 or > 1*
- *Geographical Region: Europe or Rest of the World*
- *Body mass index (kg/m2) at Screening: < 30 or ≥ 30*
- *Diabetes mellitus at Screening: 'None or diet controlled', 'Uncomplicated' or 'End-organ damage'*
- *Hypertension at Screening: Yes or No*

# 4. LISTINGS

**Listing 16.2.1.1 Patient Disposition (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Randomization Date | Treatment Start Date/Time<br>Treatment End Date/Time (Day) [b] | Treatment Completion Status or Reason for Treatment Discontinuation | End of Study Date (Day) [b] | Study Completion Status or Reason for Study Discontinuation |
|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY/HH:MM<br>DDMMMYYYY/ HH:MM (XX) | XXXXXXXXXX | DDMMMYYYY (XX) | XXXXXXXXXX |
| 123-456789 | 45/M/W | 02JUN2019 | 02JUN2019/13:50<br>05JUN2019/12:30 (11) | ADVERSE EVENT: XXXXXXXX | 11JUN2019 (10) | OTHER: XXXXXXXXXXX |
| 123-456799 | 66/F/BA | 12JUL2019 | 12JUL2019/13:55<br>15JUL2019/09:15 (399) | OTHER: XXXXXXXXXXXXXX | 11AUG2020 (31) | COMPLETED |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LDS001.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.1.2 Screen Failure Patients (Screened Patients)**

| Site ID - Patient ID | Age/Sex/Race [a] | Date of Screen Failure | Reason for Screen Failure |
|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYY | xxxxxxxxxxxxxxxxxxxxxx |
| 123-456789 | 45/M/W | 09APR2018 | Participant deemed ineligible per the protocol-defined inclusion/exclusion criteria |
| 123-456799 | 66/F/BA | 25APR2018 | Other: XXXXXXXXXXXXXXXXX |
| etc. | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LDS002.*
- *Include only screen failure patients.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.1.3 Randomization Assignments (Intent-To-Treat Population)**

| Site ID - Patient ID | Age/Sex/Race [a] | Inform Consent Date | Randomization Date | Administration of any Allowed Antiviral per Protocol | Geographical Region | Charlson Comorbidity Index | Pre-Baseline Barthel Index | Randomized Treatment | Actual Treatment |
|---|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY | XXXXXXXXX | XXXXXXXXX | XXXXXX | XXXXXX | XXXXXX | XXXXXX |
| 123-456789 | 45/M/W | 02JUN2019 | 03JUN2019 | | Europe | 0-1 | <90 | Plitidepsin 2.5mg | Plitidepsin 2.5mg |
| 123-456791 | 66/F/BA | 12JUL2019 | 13JUL2019 | | Rest of the World | 2 or Greater | ≥90 | Plitidepsin 1.5mg | Plitidepsin 2.5mg |
| 123-456799 | 46/F/B | 10JUU2020 | 16JUL2019 | Yes, Remdesivir | Europe | 2 or Greater | ≥90 | Control Arm | Control Arm |
| etc. | | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LDS003.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.1.4 Patients with Treatment Misallocation at or after Randomization (Intent-To-Treat Population)**

| Site ID - Patient ID | Age/Sex/Race [a] | Treatment assigned by IRT | Actual Treatment Received | Misallocated Treatment Start Date (Day)/ End Date (Day) [b] | Duration of Misallocated Treatment (days) [c] |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxx/xxxxxxx | xxxxxx/xxxxxxx | DDMMMYYYY (XX)/ DDMMMYYYY (XX) | XX |
| 123-456789 | 45/M/W | Treatment A | Treatment B | 02JUN2019 (66)/ 12JUN2019 (77) | 12 |
| 123-456799 | 66/F/BA | Treatment B | Treatment A | 13MAY2019 (1)/ 13JUN2019 (32) | 32 |
| etc. | | | | | |

IRT = Interactive Response Technology.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] Duration of misallocated treatment (days) = (misallocated treatment end date - misallocated treatment start date) + 1.

*Programming notes (not part of the listing):*

- *Listing template LDS003.*
- *Include only patients with treatment misallocation at or after randomization.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.1.5 Patients with Mis-Stratification (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Randomisation Stratification Factor | Stratification level as Recorded in IRT system | Stratification level as Recorded in EDC system |
|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxxxxxxx | xxxxxxxx | xxxxxxxxxx |
| 123-456789 | 45/M/W | Charlson Comorbidity Index | 0-1 | >1 |
| | | Pre-Baseline Barthel Index | <90 | ≥90 |
| 123-456799 | 66/F/BA | Charlson Comorbidity Index | 2 or Greater | 0-1 |
| etc. | | | | |

IRT = Interactive Response Technology; EDC = Electronic Data Capture.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LDS004.*
- *Include only patients who were mis-stratified.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.2.1 Inclusion and Exclusion Criteria Not Met (Screened Patients)**

| Site ID - Patient ID | Age/Sex/Race [a] | Date of Informed Consent | Protocol Version | Criterion ID not Met | Criterion Description |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | XXX | XXXXX | xxxxxxx |
| 123-456799 | 66/F/BA | 07JUN2019 | 3.0 | IN004 | More than 10 days from onset of COVID 19 symptoms to initiation of study treatment on Day 1 |
| | | | | EX011 | Pre existing neuropathies of any type Grade ≥2 according to NCI-CTCAE v5.0 |
| 123-456789 | 45/M/W | 01MAY2019 | 4.0 | EX007 | Patients receiving treatment with chloroquine or derivatives within 8 weeks before enrolment or during the study |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LIE001.*
- *Include only patients who failed at least one inclusion/exclusion criteria.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.2.2 Patients with Important Protocol Deviations (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Protocol Deviation Date (Day) [b] | Deviation Category | Deviation Details | Led to Exclusion from Per Protocol Population? [c] |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY (XX) | xxxxxxxxxxxxx | xxxxxxxxxxxx | xxx |
| 123-456789 | 45/M/W | 21AUG2018 (123) | Study Conduct/ Procedures | Failure to complete or comply with inclusion/exclusion criteriax | Yes |
| 123-456799 | 66/F/BA | 17AUG2020 (102) | Study Conduct/ Procedures | Administration Use of prohibited medication | No |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] Patients may be excluded from the Per Protocol Population for reasons not captured as protocol deviations.

*Programming notes (not part of the listing):*

- *Listing template LPD001.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.3.1 Patients Excluded from Analysis Populations (Intent-To-Treat Population)**

| Site ID - Patient ID | Age/Sex/Race [a] | FAS Population | Reason(s) for Exclusion from FAS Population | PP Population | Reason(s) for Exclusion from PP Population | As Treated Population | Reason(s) for Exclusion from As Treated Population |
|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXX | | XXX | | XXX | |
| 123-456789 | 45/M/W | Yes | - | No | Prohibited Medication during the study | Yes | - |
| 123-456799 | 66/F/BA | Yes | - | Yes | - | Yes | - |
| etc. | | | | | | | |

FAS = Full Analysis Set, PP = Per Protocol.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LDS006.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.3.2 Patient Visits and Dates (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Visit Date (Day) [b] | Patient Currently Hospitalised |
|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXXXXX | DDMMMYYYY (XX) | XXX |
| | | XXXXXXXXXXXX | DDMMMYYYY (XX) | XXX |
| | | XXXXXXXXXXXX | DDMMMYYYY (XX) | XXX |
| | | XXXXXXXXXXXX | DDMMMYYYY (XX) | XXX |
| 123-456789 | 45/M/W | Screening | 01FEB2020 (-1) | Yes |
| | | Day 1 | 02FEB2020 (1) | Yes |
| | | Day 2 | 03FEB2020 (2) | Yes |
| | | Day 3 | 04FEB2020 (3) | Yes |
| | | Day 4 | 05FEB2020 (4) | Yes |
| | | Day 5 | 06FEB2020 (5) | Yes |
| 123-456799 | 66/F/BA | Screening | 03MAR2020 (-1) | Yes |
| | | Day 1 | 04MAR2020 (1) | Yes |
| | | Day 2 | 05MAR2020 (2) | Yes |
| | | Day 3 | 06MAR2020 (3) | Yes |
| | | Day 4 | 07MAR2020 (4) | Yes |
| | | Day 5 | 08MAR2020 (5) | Yes |
| | | Day 6 | 09MAR2020 (6) | Yes |
| | | Day 7 | 10MAR2020 (7) | Yes |
| | | Day 8 | 11MAR2020 (8) | Yes |
| | | Unscheduled (1) | 13MAR2020 (10) | No |
| | | Day 15 | 18MAR2020 (15) | No |
| | | Day 31 | 03APR2020 (31) | No |
| etc. | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LSV001.*
- *Order by Site ID - Patient ID and then by Visit*

**Listing 16.2.4.1 Demographics Characteristics (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Race Other | Year of Birth | Ethnicity | Height (cm) at Screening | Weight (kg) at Screening | Body Mass Index (kg/m2) at Screening | Body Surface Area (m^2) at Screening |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXX | YYYY | XXXXXXXX | XXX.X | XXX.X | XX.X | XX.X |
| 123-456789 | 41/M/W | | 1977 | HISPANIC OR LATINO | 177.1 | 70 | 22.32 | 1.86 |
| 123-456799 | 69/F/BA | | 1948 | NOT HISPANIC OR LATINO | 165.7 | 82.1 | 29.9 | 1.90 |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LDM001.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.4.2 Baseline Characteristics (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Childbearing Potential | Chest Imaging at Day 1 | Systolic Blood Pressure (mmHg) at Screening | Diastolic Blood Pressure (mmHg) at Screening | Pulse Rate (beats/min) at Screening | Temperature (C) at Screening | Respiration Rate (breaths/min) at Screening | Oxygen Saturation at Room Air (%) at Screening |
|---|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX | XXXXXXXXX | XXX | XXX | XXX | XX.X | XXX | XX.X |
| 123-456789 | 45/M/W | NA | | 132 | 87 | 90 | 36.5 | 22 | 93.0 |
| 123-456799 | 66/F/BA | No, Surgically Sterile/ Post Menopausal | Pulmonary Infiltrates | 129 | 85 | 92 | 37.0 | 23 | 94.0 |
| etc. | | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LDM002.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.4.3 Medical History (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class<br>Grouped Preferred Term<br>Medical History Term | Start Date (Day) [b] | End Date (Day) [b] or Ongoing |
|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxxxxx | DDMMMYYYY (XX) | DDMMMYYYY (XX) |
| 123-456789 | 45/M/W | Cardiac pacemaker insertion/<br>Surgical and medical procedures/<br>Cardiac pacemaker insertion | 12JUN2019 (-11) | ONGOING |
| 123-456799 | 66/F/BA | Constipation/<br>Gastrointestinal disorders/<br>Constipation | --MAY2019 | 15MAY2019 (-8) |
| etc. | | | | |

Note: MedDRA version &meddra.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LMH001.*
- *List only patients with medical history data.*
- *Ongoing medical history should be listed with 'ONGOING' in the 'End Date' column.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*
- *Order by Site ID - Patient ID and then by start date of medical history.*

**Listing 16.2.4.4 Prior Medications (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | WHO ATC Level 2/ WHO ATC Level 4/ Grouped Preferred Term / Verbatim Text | Dose/Unit/ Frequency/ Route | Indication | Start Date (Day)/ End Date (Day) [b]/ Duration (Days) |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxxxxx | xxxxxxx/<br>xxxxxxxx/<br>xxxxxxxx | xxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX |
| 123-456789 | 45/M/W | ANGIOTENSIN II ANTAGONISTS, PLAIN/<br>ANGIOTENSIN II ANTAGONISTS, PLAIN/<br>AZILSARTAN/<br>AZILSARTAN | 20/ mg/<br>QD/<br>ORAL | Medical History: Hypertension | --APR2017 /<br>04JAN2018 (-57) / |
| 123-456799 | 66/F/BA | QUINOLONE ANTIBACTERIALS/<br>FLUOROQUINOLONES/<br>SITAFLOXACIN/<br>SITAFLOXACIN | 100/ mg/<br>QD/<br>ORAL | Medical History: Bacterial Infection | 16APR2018 (-51) /<br>20APR2018 (-47) /<br>5 |
| etc. | | | | | |

WHO = World Health Organization, ATC = Anatomical Therapeutic Chemical.
Notes: Prior medications are those taken prior to the first dose date of any study drug administration, and with a stop date before first dose date of any study drug administration.
Prior medications were coded using WHODrug Global, &whodrug.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LCM001.*
- *List only patients with prior medication data.*
- *Order by Site ID - Patient ID.*
- *Assign the version of WHO Drug Dictionary to &whodrug. macro variable as Format Bx, Version Month YYYY and update the version of WHO Drug Dictionary used for coding as needed.*

**Listing 16.2.4.5 Concomitant Medications, excluding COVID-19 Antiviral Therapies or Immunomodulatory Concomitant Medications (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | WHO ATC Level 2/<br>WHO ATC Level 4/<br>Grouped Preferred Term /<br>Verbatim Text | Dose/Unit/<br>Frequency/<br>Route | Indication | Start Date (Day)/<br>End Date (Day) [b]/<br>Duration (Days) |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxxxxxx | xxxxxxx/<br>xxxxxxxx/<br>xxxxxxxx | xxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX |
| 123-456789 | 45/M/W | ANGIOTENSIN II ANTAGONISTS, PLAIN/<br>ANGIOTENSIN II ANTAGONISTS, PLAIN/<br>AZILSARTAN/<br>AZILSARTAN | 20/ mg/<br>QD/<br>ORAL | Medical History:<br>Hypertension | --APR2017 /<br>ONGOING / |
| 123-456799 | 66/F/BA | QUINOLONE ANTIBACTERIALS/<br>FLUOROQUINOLONES/<br>SITAFLOXACIN/<br>SITAFLOXACIN | 100/ mg/<br>QD/<br>ORAL | Adverse Event: Bacterial<br>Infection | 16APR2019 (17) /<br>20APR2019 (21) /<br>5 |
| etc. | | | | | |

WHO = World Health Organization, ATC = Anatomical Therapeutic Chemical.
Notes: Concomitant medications are those with a start date on or after the first dose date of any study drug administration, or those with a start date before the first dose date of any study drug administration and a stop date on or after the first dose date of any study drug administration or ongoing end of study.
Concomitant medications were coded using WHODrug Global, &whodrug.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LCM002.*
- *List only patients with concomitant medication data.*
- *Ongoing concomitant medication should be listed with 'ONGOING' in the 'End Date' column.*
- *Order by Site ID - Patient ID.*
- *Assign the version of WHO Drug Dictionary to &whodrug. macro variable as Format Bx, Version Month YYYY and update the version of WHO Drug Dictionary used for coding as needed.*

**Listing 16.2.4.6 Diagnostic and Non-Diagnostic Procedures/Tests (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class<br>Preferred Term<br>Procedure or Test Name | Date of Procedure/<br>Test (Day) [b]/ | Indication | Result (Unit) |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxxxxx | DDMMMYYYY (XX) | XXXXXXXXX: XXXXXXXXXX | XX.X (XX) |
| etc. | | | | | |

Note: MedDRA version &meddra.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LMH001.*
- *List only patients with diagnostic and non-diagnostic procedures/tests data.*
- *Order by Site ID - Patient ID.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Listing 16.2.4.7 Subsequent COVID-19 Antiviral Therapies or Immunomodulatory Concomitant Medications (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | WHO ATC Level 2/<br>WHO ATC Level 4/<br>Grouped Preferred Term /<br>Verbatim Text | Dose/Unit/<br>Frequency/<br>Route | Indication | Start Date (Day)/<br>End Date (Day) [b]/<br>Duration (Days) |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxxxxxxxxx | xxxxxxx/<br>xxxxxxxx/<br>xxxxxxxx | COVID-19 | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX |
| etc. | | | | | |

WHO = World Health Organization, ATC = Anatomical Therapeutic Chemical.
Notes: Antiviral Therapies or Immunomodulatory concomitant medications are those with a start date on or after the first dose date of any study drug administration, or those with a start date before the first dose date of any study drug administration and a stop date on or after the first dose date of any study drug administration or ongoing end of study
Antiviral Therapies or Immunomodulatory concomitant medications were coded using WHODrug Global, &whodrug.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LCM002.*
- *List only patients with concomitant medication data.*
- *Ongoing concomitant medication should be listed with 'ONGOING' in the 'End Date' column.*
- *Order by Site ID - Patient ID.*
- *Assign the version of WHO Drug Dictionary to &whodrug. macro variable as Format Bx, Version Month YYYY and update the version of WHO Drug Dictionary used for coding as needed.*

**Listing 16.2.4.8 COVID-19 Screen and Vaccination (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Date of Qualitative PCR or Antigen Test (Day) | Result | Type of Variant | COVID-19 Vaccinated? | Fully Vaccinated | Last Shot Date (Day) | Vaccine Brand Name |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY (XX) | xxxxxxx | xxxxxxx | xxx | | | |
| 123-456789 | 45/M/W | 12JUN2019 (-5) | Positive | Delta | Yes | No | 24FEB2019 (-108) | Other: XXXXXXX |
| 123-456799 | 66/F/BA | 12JUL2019 (-4) | Positive | Other: XXXXXXX | No | | | |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LMH002.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.4.9 COVID-19 Signs and Symptoms (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Onset Date of COVID-19 Symptoms (Day) | Sign/Symptom | Response |
|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY (XX) | xxxxxxxxxxx<br>xxxxxxxxxxx<br>xxxxxxxxxxx<br>etc. | XXX<br>XXX<br>XXX |
| 123-456789 | 45/M/W | 12JUN2019 (-5) | History of fever<br>Cough<br>Sore throat<br>Runny nose (rhinorrhoea)<br>etc. | YES<br>YES-non-productive<br>NO<br>NO |
| etc. | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LMH002.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.5.1 Study Treatment Exposure (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Randomization Date | Plitidepsin<br>Start Date/Time<br>End Date/Time<br>Exposure Duration (Days) [b] | Dexamethasone<br>Start Date/Time<br>End Date/Time<br>Exposure Duration (Days) [b] | Remdesivir<br>Start Date/Time<br>End Date/Time<br>Exposure Duration (Days) [b] | Favipiravir<br>Start Date/Time<br>End Date/Time<br>Exposure Duration (Days) [b] |
|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY/ HH:MM<br>DDMMMYYYY/ HH:MM<br>XX | DDMMMYYYY/ HH:MM<br>DDMMMYYYY/ HH:MM<br>XX | DDMMMYYYY/ HH:MM<br>DDMMMYYYY/ HH:MM<br>XX | DDMMMYYYY/ HH:MM<br>DDMMMYYYY/ HH:MM<br>XX |
| 123-456789 | 45/M/W | 01FEB2018 | 01FEB2018/10:00<br>03FEB2018/11:30<br>3 | 01FEB2018/09:30<br>10FEB2018/09:30<br>10 | NA<br>NA | NA<br>NA |
| etc. | | | | | | |

NA = Not Applicable.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Duration of exposure of each study drug, i.e. plitidepsin, dexamethasone, and the regulatory-approved antiviral for those patients randomised to the control arm (ie, remdesivir or favipiravir), is defined in days as (date of last dose of the relevant study drug taken - date of first dose of the relevant study drug taken + 1).

*Programming notes (not part of the listing):*

- *Listing template LEX001.*
- *Order by Site ID - Patient ID and dose start date.*

**Listing 16.2.5.2 Study Treatment Infusion/Dose Details (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Study Drug (Route) | Infusion/Dose Start Date/Time | Infusion Stop Date/Time | Targeted Dose (unit) | Total Amount Administered | Infusion Interrupted | Reason for Infusion Interruption | Any Dose Reduction |
|---|---|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxx | xxxxxxxxx | DDMMYYYY /HH:MM | DDMMYYYY /HH:MM | XXX | XXX, xxxxxx | XXX, xxxxxxxxx | xxxxxxxxxx | XXX, xxxxxx |
| 123-456789 | 45/M/W | Day 1 | Dexamethasone (IV) | 30MAR2018 /09:30 | | 8 mg | No, Medication Error | | | |
| | | | Plitidepsin | 30MAR2018 /10:00 | 30MAR2018 /11:00 | 1.5 mg | Yes | No | | |
| | | Day 2 | Dexamethasone (IV) | 01APR2018 /09:25 | | 8 mg | Yes | | | |
| | | | Plitidepsin | 01APR2018 /09:55 | 01APR2018 /11:55 | 1.5 mg | Yes | Yes, Infusion Stopped and Restarted at a lower rate | Other: xxxxxxx | |
| | | Day 3 | Dexamethasone (IV) | 02APR2018 /09:35 | | 8 mg | Yes | | | |
| | | | Plitidepsin | 02APR2018 /10:05 | 02APR2018 /11:05 | 1.5 mg | Yes | No | | |
| | | Day 4 | Dexamethasone (Oral) | 03APR2018 /10:05 | | 6 mg | Yes | | | |
| | | Day 5 | Dexamethasone (Oral) | 04APR2018 /10:05 | | 6 mg | No, Other: xxxxx | | | |
| | | Day 6 | Dexamethasone (Oral) | No, Dexa treatment completed | | | | | | |
| etc. | | | | | | | | | | |

IV = Intravenous.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LDA002.*
- *Unknown End time should be listed with 'UK:UK' as 'End time'.*
- *Include all Visits available in data including any unscheduled visits.*
- *If any Study Drug was not administered, display 'No' and the corresponding reason separated by comma, ie 'No, xxxxxxxxxxxxx' in the 'Infusion/Dose Start Date/Time' column.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.6.1 11-point WHO Clinical Progression Scale (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Date of Measurement (Day) [b] | Value |
|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXX | DDMMMYYYY (XX) | xxx |
| 123-456789 | 45/M/W | Screening | 03MAR2020 (-1) | 5 |
| | | Day 1 | 04MAR2020 (1) | 5 |
| | | Day 2 | 05MAR2020 (2) | 5 |
| | | Day 3 | 06MAR2020 (3) | 5 |
| | | Day 4 | 07MAR2020 (4) | 5 |
| | | Day 5 | 08MAR2020 (5) | 5 |
| | | Day 6 | 09MAR2020 (6) | 5 |
| | | Day 7 | 10MAR2020 (7) | 4 |
| | | Day 8 | 11MAR2020 (8) | 2 |
| | | Day 15 | 18MAR2020 (15) | 1 |
| | | Day 31 | 03APR2020 (31) | 0 |
| etc. | | | | |

Notes: 11-point WHO Clinical Progression Scale, where 0= uninfected, no viral RNA detected; 1 = asymptomatic, viral RNA detected; 2 = symptomatic, independent; 3 = symptomatic, assistance needed; 4 = hospitalised, no oxygen therapy (if hospitalised for isolation only, record status as for ambulatory patient); 5 = hospitalised, oxygen by mask or nasal prongs; 6 = hospitalised, oxygen by NIV or high flow; 7 = intubation and mechanical ventilation, pO2/FIO2 ≥150 or SpO2/FIO2 ≥200; 8 = mechanical ventilation, pO2/FIO2<150 (SpO2/FIO2 <200) or vasopressors; 9 = mechanical ventilation, pO2/FIO2<150 and vasopressors, dialysis or ECMO; 10 = dead.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEF001.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.6.2 Functional Status-Barthel Index (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Date of Assessment (Day) [b] | Total Score |
|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXX | DDMMMYYYY (XX) | xxx |
| 123-456789 | 45/M/W | Previous Month to COVID-19 Infection | | 100 |
| | | Screening | 03MAR2020 (-1) | 85 |
| | | Day 8 | 11MAR2020 (8) | 90 |
| | | Hospital Discharge | 14MAR2020 (11) | 95 |
| | | Day 15 | 18MAR2020 (15) | 95 |
| | | Day 31 | 03APR2020 (31) | 100 |
| etc. | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEF001.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.6.3 Hospitalization for COVID-19 (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| | | | | Hospital Status Change | | |
|---|---|---|---|---|---|---|
| **Site ID - Patient ID** | **Age/Sex/Race [a]** | **Initial Date/Time of Admission for COVID-19 (Day) [b]** | **Initially Admitted to Unit** | **Date/Time of Change (Day) [b]** | **Hospital Status** | **Reason** |
| XXXX-YYYYY | XX/X/X | DDMMMYYYY/HH:MM (XX) | xxxxxxxxxxxxxxx | DDMMMYYYY/HH:MM (XX) | xxxxxxxxxxxxxxx | xxxxxxxxxxxxxxx |
| 123-456789 | 45/M/W | 27FEB2018 /12:40 (-3) | Regular Ward | 03MAR2018/12:30 (2) | ICU | Related to study disease – worsening |
| | | | | 06MAR2018/12:30 (5) | Regular ward | Related to study treatment – improvement |
| | | | | 11MAR2018/12:30 (10) | Discharge from hospital | Related to study disease – improvement |
| etc. | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEF001.*
- *Order by Site ID - Patient ID and Date/Time of Change.*

**Listing 16.2.6.4 Oxygen status (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Altitude (m) | Date/Time of Assessment/ Change (Day) [b] | Oxygen Status | SpO2 (%) | FiO2 (%) | PaO2 (mmHg) | PaO2/FiO2 adjusted by Altitude |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxx | DDMMMYYYY/HH:MM (XX) | xxxxxxxxxxxxxxx | xxxx | xxxx | xxxx | xxxx |
| 123-456789 | 45/M/W | 759 | 02MAR2018/12:30 (1) | High flow oxygen | 93.5 | 40 | 67 | 167.5 |
| | | | 06MAR2018/12:30 (5) | Low flow oxygen | 95.7 | 45 | 85 | 188.9 |
| | | | 11MAR2018/12:30 (10) | No supplemental oxygen needed | 98.1 | 50 | 98 | 196.0 |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEF001.*
- *Order by Site ID - Patient ID and Date/Time of Assessment/ Change.*

**Listing 16.2.6.5 Time to Sustained Withdrawal of Oxygen Supplementation (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Time to Event Origin Date | Analysis Date (time to Event (Days)) [b] | Censored | Event or Censoring Description |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY (XXX) | XXX | XXXXXXXXX |
| 123-456789 | 45/M/W | 10JAN2007 | 26JAN2007 (17) | No | Sustained withdrawal of oxygen supplementation |
| 123-456799 | 66/F/BA | 01JAN2007 | 15JAN2007 (15) | Yes | Early study discontinuation |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the randomization date.

*Programming notes (not part of the listing):*

- *Listing template LEF002.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.6.6 Time to Sustained Hospital Discharge (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Time to Event Origin Date | Analysis Date (time to Event (Days)) [b] | Censored | Event or Censoring Description |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY (XXX) | XXX | XXXXXXXXX |
| 123-456789 | 45/M/W | 10JAN2007 | 26JAN2007 (17) | No | Sustained Hospital Discharge |
| 123-456799 | 66/F/BA | 01JAN2007 | 15JAN2007 (15) | Yes | Death |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the randomization date.

*Programming notes (not part of the listing):*

- *Listing template LEF002.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.6.7 Overall Survival (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Time to Event Origin Date | Analysis Date (time to Event (Days)) [b] | Censored | Event or Censoring Description |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY (XXX) | XXX | XXXXXXXXX |
| 123-456789 | 45/M/W | 10JAN2007 | 26JAN2007 (17) | No | Death |
| 123-456799 | 66/F/BA | 01JAN2007 | 15JAN2007 (15) | Yes | Last known to be Alive Date |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the randomization date.

*Programming notes (not part of the listing):*

- *Listing template LEF002.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.6.8 COVID-19 Viral Load ($log_{10}$ copies/mL) (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Date /Time of Collection (Day) [b] | Value | Change from Day 1 |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXX | DDMMMYYYY/HH:MM (XX) | xxx | xxx |
| 123-456789 | 45/M/W | Day 1 | 19JAN2018/10:30 (1) | 6.1 | |
| | | Day 8 | 26JAN2018/10:30 (8) | 2.5 | -3.6 |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEF001.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.6.9 Anti-SARS-CoV-2 IgG (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Date /Time of Collection (Day) [b] | Result | Ratio Value | % Change from Day 1 |
|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXX | DDMMMYYYY/HH:MM (XX) | XXXXXX | xxx | xxx |
| 123-456789 | 45/M/W | Day 1 | 19JAN2018/10:30 (1) | Negative | <0.8 | |
| | | Day 31 | 18FEB2018/10:30 (31) | Borderline | 1.0 | 0.6 |
| etc. | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEF001.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.6.10 Time to Intensification of Respiratory Support (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Time to Event Origin Date | Analysis Date (time to Event (Days)) [b] | Censored | Event or Censoring Description |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY (XXX) | XXX | XXXXXXXXX |
| 123-456789 | 45/M/W | 10JAN2007 | 26JAN2007 (17) | No | Therapy Intensification |
| 123-456799 | 66/F/BA | 01JAN2007 | 15JAN2007 (15) | Yes | Last Visit or Telephone Contact |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the randomization date.

*Programming notes (not part of the listing):*

- *Listing template LEF002.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.6.11 Time to Sustained Withdrawal of Oxygen Supplementation - Adding Oxygen Supplementation Status (Intent-To-Treat Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Time to Event Origin Date | Analysis Date (time to Event (Days)) [b] | Censored | Event or Censoring Description |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | DDMMMYYYY | DDMMMYYYY (XXX) | XXX | XXXXXXXXX |
| 123-456789 | 45/M/W | 10JAN2007 | 26JAN2007 (17) | No | Sustained withdrawal of oxygen supplementation |
| 123-456799 | 66/F/BA | 01JAN2007 | 15JAN2007 (15) | Yes | Early study discontinuation |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the randomization date.

*Programming notes (not part of the listing):*

- *Listing template LEF002.*
- *Order by Site ID - Patient ID.*

**Listing 16.2.7.1 Adverse Events (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class/ Grouped Preferred Term/ Verbatim | Start Date (Day)/ Stop Date (Day) [b]/ Duration (Days) or Ongoing | TEAE [c] | Severity/ Seriousness criteria | Relationship to Study Treatment | Action taken to Plitidepsin/ Dexamethasone/ Antiviral Control Arm [d] | Outcome |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX | | Grade X/<br>xxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | xxxxxxxxxxxx |
| 123-456789 | 45/M/W | Infections and infestations/<br>Pharyngitis/<br>Acute Pharyngitis | 19JUL2018 (56)/<br>24JUL2018 (61)/<br>6 | * | Grade 2/ | Yes - Related to Dexamethasone | Not Applicable/<br>Not changed/<br>Omitted | Recovered/ Resolved |
| | | Musculoskeletal and connective tissue disorders/<br>Periarthritis/<br>Shoulder Periarthritis(Both) | 14AUG2018 (82)/<br>ONGOING | * | Grade 3/<br>Life Threatening | No - Study disease | Not Applicable/<br>Not changed/<br>Unknown | Recovering/ Resolving |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] TEAE=Treatment Emergent Adverse Event. TEAEs are flagged with *.
[d] Antiviral control arm is the regulatory-approved antiviral for those patients randomised to the control arm, i.e., remdesivir or favipiravir.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE001.*
- *Order by Site ID - Patient ID and AE No.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Listing 16.2.7.2 Adverse Events with Severity Grade ≥ 3 (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class/ Grouped Preferred Term/ Verbatim | Start Date (Day)/ Stop Date (Day) [b]/ Duration (Days) or Ongoing | TEAE [c] | Severity/ Seriousness criteria | Relationship to Study Treatment | Action taken to Plitidepsin/ Dexamethasone/ Antiviral Control Arm [d] | Outcome |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xx/<br>xxxxxxxxxxxxxx/<br>xxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX | | Grade X/<br>xxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | xxxxxxxxxxxx |
| 123-456789 | 45/M/W | Infections and infestations/<br>Pharyngitis/<br>Acute Pharyngitis | 19JUL2018 (56)/<br>24JUL2018 (61)/<br>6 | * | Grade 3/ | Yes - Related to Dexamethasone | Not Applicable/<br>Not changed/<br>Omitted | Recovered/ Resolved |
| | | Musculoskeletal and connective tissue disorders/<br>Periarthritis/<br>Shoulder Periarthritis(Both) | 14AUG2018 (82)/<br>ONGOING | * | Grade 4/<br>Life Threatening | No - Study disease | Not Applicable/<br>Not changed/<br>Unknown | Recovering/ Resolving |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] TEAE=Treatment Emergent Adverse Event. TEAEs are flagged with *.
[d] Antiviral control arm is the regulatory-approved antiviral for those patients randomised to the control arm, i.e., remdesivir or favipiravir.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE001.*
- *Order by Site ID - Patient ID and AE No.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Listing 16.2.7.3 Adverse Events Resulting in Death (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class/ Grouped Preferred Term/ Verbatim | Start Date (Day)/ Stop Date (Day) [b]/ Duration (Days) or Ongoing | TEAE [c] | Severity/ Seriousness criteria | Relationship to Study Treatment | Action taken to Plitidepsin/ Dexamethasone/ Antiviral Control Arm [d] | Outcome |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX | | Grade X/<br>xxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | xxxxxxxxxxxx |
| 123-456789 | 45/M/W | Musculoskeletal and connective tissue disorders/<br>Periarthritis/<br>Shoulder Periarthritis(Both) | 14AUG2018 (82)/<br>24AUG2018 (61)/<br>15 | * | Grade 5/<br>Death | No - Study disease | Not Applicable/<br>Dose not Changed/<br>Dose not Changed | Fatal |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] TEAE=Treatment Emergent Adverse Event. TEAEs are flagged with *.
[d] Antiviral control arm is the regulatory-approved antiviral for those patients randomised to the control arm, i.e., remdesivir or favipiravir.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE001.*
- *Order by Site ID - Patient ID and AE No.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Listing 16.2.7.4 Adverse Events of Special Interest (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | System Organ Class/ Grouped Preferred Term/ Verbatim | Start Date (Day)/ Stop Date (Day) [b]/ Duration (Days) or Ongoing | TEAE [c] | Severity/ Seriousness criteria | Relationship to Study Treatment | Action taken to Plitidepsin/ Dexamethasone/ Antiviral Control Arm [d] | Outcome |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxx/<br>xxxxxxxxxxxxxx | DDMMMYYYY (XX)/<br>DDMMMYYYY (XX)/<br>XX | | Grade X/<br>xxxxxx | xxxxxxxxxxxx | xxxxxxxxxxxxxx/<br>xxxxxxxxxxxxx/<br>xxxxxxxxxxxxx | xxxxxxxxxxxx |
| 123-456789 | 45/M/W | Musculoskeletal and connective tissue disorders/<br>Periarthritis/<br>Shoulder Periarthritis(Both) | 14AUG2018 (82)/<br>24AUG2018 (61)/<br>15 | * | Grade 5/<br>Death | No - Study disease | Not Applicable/<br>Dose not Changed/<br>Dose not Changed | Fatal |
| etc. | | | | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative day to the start date of study treatment.
[c] TEAE=Treatment Emergent Adverse Event. TEAEs are flagged with *.
[d] Antiviral control arm is the regulatory-approved antiviral for those patients randomised to the control arm, i.e., remdesivir or favipiravir.
MedDRA version &meddra.

*Programming notes (not part of the listing):*

- *Listing template LAE001.*
- *Order by Site ID - Patient ID and AE No.*
- *Assign the version of MedDRA Dictionary to &meddra. macro variable as XX.X and update the version of MedDRA Dictionary used for coding as needed.*

**Listing 16.2.8.1.1 Laboratory Results - Haematology (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Parameter (unit) | Visit | Date of Collection (Day) [b] | Value* (L) (H) | Reference Range | Change from Baseline | NCI-CTCAE |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX (XXXX) | XXXXXXXXX | DDMMMYYYY (XX) | XXXX | XXX-XXX | XXXX | X |
| 123-456789 | 45/M/W | Red Blood Cell Count (TI/L) | Screening | 19JAN2018 (-1) | 24.20 | 5-40 | | |
| | | | Day 1 | 20JAN2018 (1) | 24.39* | 5-40 | | |
| | | | Day 2 | 21JAN2018 (2) | 23.91 | 5-40 | -0.48 | 2 |
| | | | Day 3 | 22JAN2018 (3) | 23.80 | 5-40 | -0.59 | 2 |
| | | Haemoglobin (g/L) | Screening | 19JAN2018 (-1) | 99 (L) | 100-150 | | |
| | | | Day 1 | 20JAN2018 (1) | 103* | 100-150 | | |
| | | | Day 2 | 21JAN2018 (2) | 99 (L) | 100-150 | -4 | 3 |
| | | | Day 3 | 22JAN2018 (3) | 98 (L) | 100-150 | -5 | 4 |
| | | Platelet Count (GI/L) | Screening | 19JAN2018 (-1) | 132 | 100-139 | | |
| | | | Day 1 | 20JAN2018 (1) | 139* | 100-139 | | |
| | | | Day 2 | 21JAN2018 (2) | 140 (H) | 100-139 | 1 | 1 |
| | | | Day 3 | 22JAN2018 (3) | 114 | 100-139 | -25 | |
| etc. | | | | | | | | |

Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
* Baseline value; (L): below lower limit of normal (LLN); (H): above upper limit of normal (ULN).
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LLB001A.*
- *Parameters are: Red Blood Cell Count, Haemoglobin, Haematocrit, White Blood Cell Count, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes, and Platelet Count.*
- *Include all Visits available in data including any unscheduled visits.*
- *Order by Site ID - Patient ID, parameter and Visit.*

**Listing 16.2.8.1.2 Laboratory Results - Serum Chemistry (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Parameter (unit) | Visit | Date of Collection (Day) [b] | Value* (L) (H) | Reference Range | Change from Baseline | NCI-CTCAE |
|---|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX (XXXX) | XXXXXXXXX | DDMMMYYYY (XX) | XXXX | XXX-XXX | XXXX | X |
| etc. | | | | | | | | |

Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
* Baseline value; (L): below lower limit of normal (LLN); (H): above upper limit of normal (ULN).
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LLB001A.*
- *Parameters are: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase, Gamma-Glutamyltransferase (GGT), Lactate Dehydrogenase (LDH), Total Bilirubin, Direct Bilirubin, Glucose (fasting), Sodium, Potassium, Calcium (adjusted), Magnesium, Creatinine, Calculated Creatinine Clearance (Cockcroft Gault equation), Albumin, Creatine Phosphokinase (CPK), Troponin T, NT-pro-BNP, Blood Urea Nitrogen, Ferritin, Amylase, Lipase, and Procalcitonin.*
- *Include all Visits available in data including any unscheduled visits.*
- *Order by Site ID - Patient ID, parameter and Visit.*

**Listing 16.2.8.1.3 Laboratory Results - Immunology (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Parameter (unit) | Visit | Date of Collection (Day) [b] | Value* (L) (H) | Reference Range | Change from Baseline |
|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX (XXXX) | XXXXXXXXX | DDMMMYYYY (XX) | XXXX | XXX-XXX | XXXX |
| etc. | | | | | | | |

Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
* Baseline value; (L): below lower limit of normal (LLN); (H): above upper limit of normal (ULN).
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LLB001A.*
- *Parameters are: C-reactive protein (CRP), ferritin, IL-1β, IL-6, IL-10, and tumour necrosis factor alpha (TNFα).*
- *Include all Visits available in data including any unscheduled visits.*
- *Order by Site ID - Patient ID, parameter and Visit.*

**Listing 16.2.8.1.4 Laboratory Results - Coagulation (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Parameter (unit) | Visit | Date of Collection (Day) [b] | Value* (L) (H) | Reference Range | Change from Baseline |
|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX (XXXX) | XXXXXXXXX | DDMMMYYYY (XX) | XXXX | XXX-XXX | XXXX |
| etc. | | | | | | | |

Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value from central Laboratory collected prior to the first dose of the first study drug administration.
* Baseline value; (L): below lower limit of normal (LLN); (H): above upper limit of normal (ULN).
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LLB001A.*
- *Parameter is: D-dimer.*
- *Include all Visits available in data including any unscheduled visits.*
- *Order by Site ID - Patient ID, parameter and Visit.*

**Listing 16.2.8.1.5 Laboratory Results - Missing NCI-CTCAE Toxicity Grades (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Parameter | Time point |
|---|---|---|---|
| XXXX-YYYYY<br>etc. | XX/X/X | XXXXXXXXX - XXX | Baseline or Post-Baseline |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.

*Programming notes (not part of the listing):*

- *Listing template LLB001A.*
- *Parameters are: Haemoglobin - Low, Haemoglobin - High, White Blood Cell Count - Low, White Blood Cell Count - High, Neutrophils - Low, Eosinophils - High, Lymphocytes - Low, Lymphocytes - High, and Platelet Count - Low, Alanine aminotransferase (ALT) - High, Aspartate aminotransferase (AST) - High, Alkaline phosphatase - High, Gamma-Glutamyltransferase (GGT) - High, Lactate dehydrogenase (LDH) - High, Total Bilirubin - High, Glucose (fasting) - Low, Sodium - Low, Sodium - High, Potassium - Low, Potassium - High, Calcium - Low, Calcium - High, Magnesium - Low, Magnesium - High, Creatinine - High, Albumin - Low, Creatine Phosphokinase (CPK) - High, Troponin T - High, Amylase - High, and Lipase - High.*
- *Order by Site ID - Patient ID, parameter and Visit.*

**Listing 16.2.8.2.1 Vital Signs and Oxygen Saturation (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Parameter (unit) | Visit | Date/Time of Collection (Day) [b] | Value* | Change from Baseline | Change from Start Infusion |
|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX (XXXX) | XXXXXXXXX | DDMMMYYYY /HH:MM (XX) | XXXX | XXXX | |
| 123-456789 | 45/M/W | SBP (mmHg) | Screening | 19JAN2018 (-1) | 132 | | |
| | | | Day 1 | 20JAN2018 (1) | 139 | | |
| | | | Day 1 – Start Infusion | 20JAN2018/09:30 (1) | 136* | | |
| | | | Day 1 – End of Infusion | 20JAN2018/11:05 (1) | 140 | | 4 |
| | | | Day 2 | 21JAN2018 (2) | 140 | 4 | |
| | | | Day 2 – Start Infusion | 21JAN2018/09:30 (2) | 138 | 2 | |
| | | | Day 2 – End of Infusion | 21JAN2018/11:05 (2) | 136 | | -2 |
| | | | Day 3 | 22JAN2018 (3) | 114 | -22 | |
| | | | Day 3 – Start Infusion | 22JAN2018/09:30 (3) | 116 | -20 | |
| | | | Day 3 – End of Infusion | 22JAN2018/11:05 (3) | 112 | | -4 |
| | | | Day 4 | 23JAN2018 (4) | 114 | -22 | |
| etc. | | | | | | | |

Notes: The baseline value is defined as last scheduled or unscheduled non-missing value collected prior to the first dose of the first study drug administration.
* Baseline value; Start Infusion = Just before the start of the plitidepsin infusion; After Infusion = Immediately at the end of the plitidepsin infusion.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LVS001A.*
- *Parameters are: Systolic Blood Pressure (mmHg); Diastolic Blood Pressure (mmHg), Pulse rate (beats/min); Temperature (°C); Respiration Rate (breaths/min), SpO2 (%), FiO2 (%) and PaO2 (mmHg).*
- *Include all Visits available in data including any unscheduled Visits.*
- *Order by Site ID - Patient ID, parameter and Visit.*

**Listing 16.2.8.3.1 12-Lead Electrocardiogram (ECG) Parameters (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Parameter (unit) | Visit – Replicate # | Date/Time of Assessment (Day) [b] | Value |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX (XXXX) | XXXXXXXXX | DDMMMYYYY /HH:MM (XX) | XXXX |
| 123-456789 | 45/M/W | PR Interval (msec) | Screening - Replicate 1 | 19JAN2018/09:25 (-1) | 228 |
| | | | Screening - Replicate 2 | 19JAN2018/09:30 (-1) | 237 |
| | | | Screening - Replicate 3 | 19JAN2018/09:35 (-1) | 223 |
| | | | Day 1 - Replicate 1 | 20JAN2018/10:05 (1) | 223 |
| | | | Day 1 - Replicate 2 | 20JAN2018/10:10 (1) | 228 |
| | | | Day 1 - Replicate 3 | 20JAN2018/10:15 (1) | 237 |
| | | QRS Interval (msec) | Screening - Replicate 1 | 19JAN2018/09:25 (-1) | 99 |
| | | | Screening - Replicate 2 | 19JAN2018/09:30 (-1) | 103 |
| | | | Screening - Replicate 3 | 19JAN2018/09:35 (-1) | 99 |
| | | QTcF Interval (msec) | Screening - Replicate 1 | 19JAN2018/09:25 (-1) | 393 |
| | | | Screening - Replicate 2 | 19JAN2018/09:30 (-1) | 377 |
| | | | Screening - Replicate 3 | 19JAN2018/09:35 (-1) | 394 |
| etc. | | | | | |

[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEG001A.*
- *Parameters are: heart rate (beats/min); RR interval (msec); PR interval (msec); QRS interval (msec); QT interval (msec); and Fridericia corrected QT (QTcF) interval (msec).*
- *Include all Visits available in data including any unscheduled Visit.*
- *The displayed xxx do not reflect actual decimal precision. Please follow Section 2.11 for rounding rules.*
- *Order by Site ID - Patient ID, parameter and Visit.*

**Listing 16.2.8.3.2 12-Lead Electrocardiogram (ECG) - Average QTcF Interval (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Date of Collection (Day) [b] | Average QTcF Interval (msec)* | > 500 msec [c] | Change from Baseline | Change from baseline > 30 msec [d] |
|---|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXXX | DDMMMYYYY (XX) | XXXX | XXX | XXXX | XXX |
| 123-456789 | 45/M/W | Screening | 19JAN2018 (-1) | 419* | | | |
| | | Day 1 | 20JAN2018 (1) | 425 | | 6 | |
| | | Day 3 | 22JAN2018 (3) | 450 | | 31 | Yes |
| | | Day 31 | 18FEB2018 (31) | 412 | | -7 | |
| etc. | | | | | | | |

Notes: The Baseline value is defined as last scheduled or unscheduled non-missing value collected prior to the first dose of the first study drug administration.
* Baseline value.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.
[c] > 500 msec column is 'Yes' if the average QTcF interval value is greater than 500 msec.
[d] Change from baseline > 30 msec column is 'Yes' if change from baseline value is greater than 30 msec.

*Programming notes (not part of the listing):*

- *Listing template LEG001B.*
- *Include all Visits available in data including any unscheduled Visit.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.8.3.3 12-Lead ECG Findings (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit – Replicate # | Date/Time of Collection (Day) [b] | ECG Interpretation | Finding |
|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXX | DDMMMYYYY /HH:MM (XX) | xxxxxxxxxxxxxxx | xxxxxxxxxxxxxxxxxxx |
| 123-456789 | 45/M/W | Screening - Replicate 1 | 19JAN2018/09:25 (-1) | Normal | |
| | | Screening - Replicate 2 | 19JAN2018/09:30 (-1) | Normal | |
| | | Screening - Replicate 3 | 19JAN2018/09:35 (-1) | Abnormal, NCS | COMPLETE LEFT BUNDLE BRANCH BLOCK |
| etc. | | | | | |

CS = clinically significant; NCS = not clinically significant.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LEG002.*
- *Include all Visits available in data including any unscheduled Visit.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.8.4.1 Physical Examination Results (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Date of Examination (Day) [b] | Any Abnormalities? | Body System | Results |
|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXX | DDMMMYYYY (XX) | XXX | XXXXXXXX | XXXXXXXX |
| 123-456789 | 45/M/W | Screening | 19JAN2018 (-1) | No | | |
| | | Day 1 | 20JAN2018 (1) | No | | |
| | | Day 2 | 21JAN2018 (2) | Yes | General Appearance | Abnormal, CS - *findings* |
| | | Day 3 | 22JAN2018 (3) | Yes | HEENT | Abnormal, NCS - *findings* |
| | | Day 4 | 23JAN2018 (4) | No | | |
| etc. | | | | | | |

HEENT = head, eyes, ears, nose, throat; CS = clinically significant; NCS = not clinically significant.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LPE001.*
- *Include all Visits available in data including any unscheduled Visit.*
- *Order by Site ID - Patient ID and Visit.*

**Listing 16.2.8.5.1 Chest Imaging (As Treated Population)**

**Treatment Group: <<Plitidepsin 2.5mg/Plitidepsin 1.5mg/Control Arm>>**

| Site ID - Patient ID | Age/Sex/Race [a] | Visit | Date of Chest Imaging (Day) [b] | Method | Interpretation | Conditions Present |
|---|---|---|---|---|---|---|
| XXXX-YYYYY | XX/X/X | XXXXXXXX | DDMMMYYYY (XX) | XXXXXX | XXXXXXXX | XXXXXXXX |
| 123-456789 | 45/M/W | Day 1 | 20JAN2018 (1) | X-RAY | Abnormal, CS | Pulmonary infiltrates, Bilateral pneumonia, Other: XXXXXXXXXXX |
| | | Day 8 | 27JAN2018 (8) | X-RAY | Normal | |
| | | Day 31 | 19FEB2018 (31) | X-RAY | Normal | |
| etc. | | | | | | |

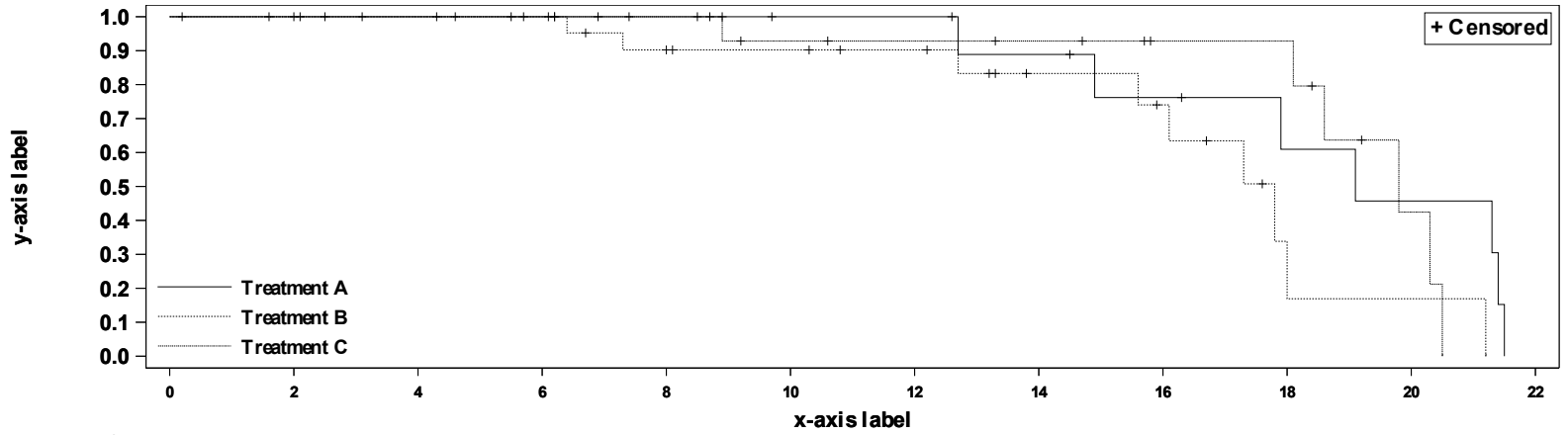
CS = clinically significant; NCS = not clinically significant.
[a] For sex, F = Female; M = Male. For race, AI = American Indian or Alaska native; A = Asian; BA = Black or African American; PI = Native Hawaiian or Other Pacific Islander; W = White; O = Other; UN = Unknown.
[b] Relative to the start of study treatment.

*Programming notes (not part of the listing):*

- *Listing template LPE001.*
- *Include all Visits available in data including any unscheduled Visit.*
- *Order by Site ID - Patient ID and Visit.*

# 5. FIGURES

**Figure 14.2.1.1 Time to Sustained Withdrawal of Oxygen Supplementation - Kaplan-Meier Plot (Intent-To-Treat Population)**




Number of subjects at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment A | 21 | 20 | 19 | 18 | 14 | 10 | 10 | 8 | 6 | 4 | 3 | 0 |
| Treatment B | 28 | 27 | 24 | 22 | 18 | 16 | 14 | 9 | 7 | 2 | 1 | 0 |
| Treatment C | 15 | 15 | 15 | 14 | 14 | 12 | 11 | 10 | 7 | 7 | 2 | 0 |

Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

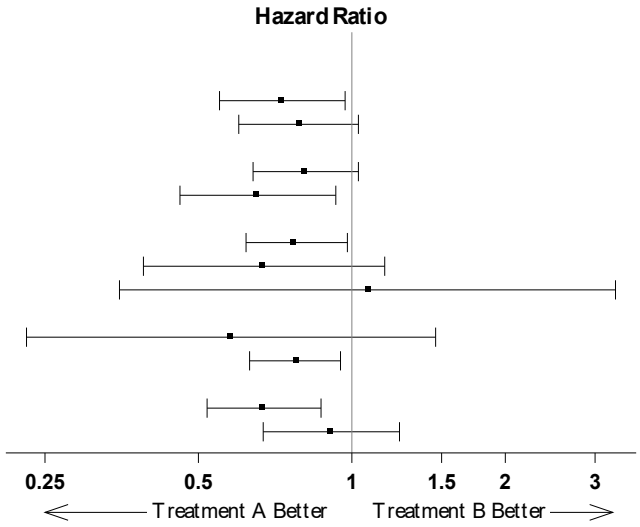
Reference: Table 14.2.1.1.1

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Kaplan-Meier Plot |
| Figure Template ID | FG002 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Time to Sustained Withdrawal of Oxygen Supplementation (days) |
| X-axis Scale | Major tick - 0-42 by 3, Minor tick - Nil |
| Y-axis label | Cumulative Proportion of Sustained Withdrawal of Oxygen Supplementation (1-Cumulative Survival) |
| Y-axis Scale | 0.0 to 1.0 by 0.1 |
| Legend | Line patterns for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear inside plot, bottom right |
| Annotations | Display 'Numbers of patients at risk' at the start of the corresponding day on the x-axis<br>Display censoring symbol legend inside plot, top left |
| Other notes | Parameter option for symbol statement: Interpol = step |

**Figure 14.2.1.2 Time to Sustained Withdrawal of Oxygen Supplementation - Subgroup Analysis - Forest Plot (Intent-To-Treat Population)**

| Subgroup | Treatment A N | Treatment B N | HR (95% CI) |
|---|---|---|---|
| **Age (years)** | | | |
| <65 | 1077 | 1091 | 0.73 (0.55, 0.97) |
| ≥65 | 862 | 846 | 0.79 (0.60, 1.03) |
| **Gender** | | | |
| Male | 1293 | 1245 | 0.81 (0.64, 1.03) |
| Female | 646 | 692 | 0.65 (0.46, 0.93) |
| **Race** | | | |
| White | 1600 | 1619 | 0.77 (0.62, 0.98) |
| Black or African American | 218 | 225 | 0.67 (0.39, 1.16) |
| Other | 88 | 60 | 1.08 (0.35, 3.29) |
| **Ethnicity** | | | |
| Hispanic or Latino | 75 | 72 | 0.58 (0.23, 1.46) |
| Not Hispanic | 1852 | 1857 | 0.78 (0.63, 0.95) |
| **Body Mass Index** | | | |
| < 30 | 1123 | 1096 | 0.67 (0.52, 0.87) |
| ≥ 30 | 810 | 835 | 0.91 (0.67, 1.24) |



*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Forest Plot |
| Figure Template ID | FG006 |
| Treatment display details | Display 2 treatment groups per page. Plitidepsin 2.5mg vs Control Arm on page 1 and Plitidepsin 1.5mg vs Control Arm on page 2. |
| X-axis label | <---------- Control Arm Better  Plitidepsin 2.5mg Better ---------> on page 1.<br><---------- Control Arm Better  Plitidepsin 1.5mg Better ---------> on page 2. |
| X-axis Scale | 0.33; 0.5; 0.66; 1; 1.5; 2; 3. |
| Y-axis label | Nil. |
| Y-axis Scale | Major tick: Nil>>, Minor tick: Nil. |
| Legend | Display 2 treatment groups per page.<br>Subgroup  Plitidepsin 2.5mg N  Control Arm N  HR [b] (95% CI)  Hazard Ratio  (on page 1)<br>Subgroup  Plitidepsin 1.5mg N  Control Arm N  HR [b] (95% CI)  Hazard Ratio  (on page 2) |
| Legend position | Top |
| Annotations | Include reference line |
| Other notes | Display subgroups as following:<br>All patients<br>Charlson Comorbidity Index<br>0 - 1<br>> 1<br>Geographical Region<br>Europe<br>Rest of the World<br>Pre-baseline Barthel index<br>≥ 90<br>< 90<br>Patients included before and after amendment<br>Protocol v.6 or before<br>Protocol v.7<br>Sex<br>Female<br>Male<br>Age at study entry (years)<br>18 to 39 |

40 to 64
≥ 65

Race
Asian
Black
White
Other

Ethnic group
Hispanic or Latino
Not Hispanic or Latino

Site location: each study site with more than 1/6 out of the randomised patients (i.e. >33 randomised patients for the futility analysis and >101 randomised patients for the final analysis) will be considered as a group and the remaining study sites, i.e. those study sites with less than 1/6 out of the randomised patients will be pooled together as a one single group
Site XXX
Site XXX
Other Sites

Use of antiviral therapies or immunomodulatory drugs through the study
Yes
No

Previous COVID-19 vaccination status
Fully vaccinated
Non-fully vaccinated
No vaccinated
Fully vaccinated + Non-fully vaccinated

Anti-SARS-CoV-2 IgG Day 1
Non-positive
Positive

Pre-randomisation dexamethasone
Yes
No

Total duration of corticoid therapy
< 9 days
[9 – 11] days
> 11 days

Total cumulative dose of corticoid therapy (dexamethasone or equivalent)
≤ 60 mg
> 60 mg

SARS-CoV-2 viral load (log10 copies/mL) at Day 1 before study drug administration
< 4
[4 - 7]

> 7
Time between onset date of COVID-19 symptoms and initiation of study treatment
≤ 5 days
6 - 10 days
> 10 days
Body mass index (kg/m2) at Screening
< 30
≥ 30
Hypertension at Screening
Yes
No
Myocardial infarction at Screening
Yes
No
Congestive heart failure at Screening
Yes
No
Peripheral vascular disease at Screening
Yes
No
Cerebrovascular disease at Screening
Yes
No
Dementia at Screening
Yes
No
Chronic obstructive pulmonary disease at Screening
Yes
No
Connective tissue disease at Screening
Yes
No
Peptic ulcer disease at Screening
Yes
No
Liver disease at Screening
None
Mild
Moderate or Severe
Diabetes mellitus at Screening
None or diet controlled

Uncomplicated
End-organ damage
Hemiplegia at Screening
Yes
No
Moderate or severe chronic kidney disease at Screening
Yes
No
Solid tumor at Screening
None
Localized
Metastatic
Leukemia at Screening
Yes
No
Lymphoma at Screening
Yes
No
AIDS at Screening
Yes
No
ISARIC-4C mortality score
Low (0 - 3)
Intermediate (4 - 8)
High (9 - 14)
Vey high (≥ 15)
ISARIC-4C deterioration probability (%)
≤ 25
(25 - 50]
> 50
LDH at Baseline
≤ ULN
> ULN
CRP (mg/L) at Baseline
≤ 100
> 100
D-dimer at Baseline
≤ ULN
> ULN
Ferritin at Baseline
≤ ULN

> ULN
Creatinine at Baseline
≤ ULN
> ULN
IL-6 at Baseline
≤ Median
> Median
IL-10 at Baseline
≤ Median
> Median
Lymphocytes count decreased at Baseline
Grade 0
Grade ≥ 1
Neutrophils/lymphocytes ratio at Baseline
< 6
≥ 6
SARS-CoV-2 variant
Alpha
Beta
Gamma
Delta
Eta
Iota
Kappa
Lambda
Mu
<Any other potential new variant>

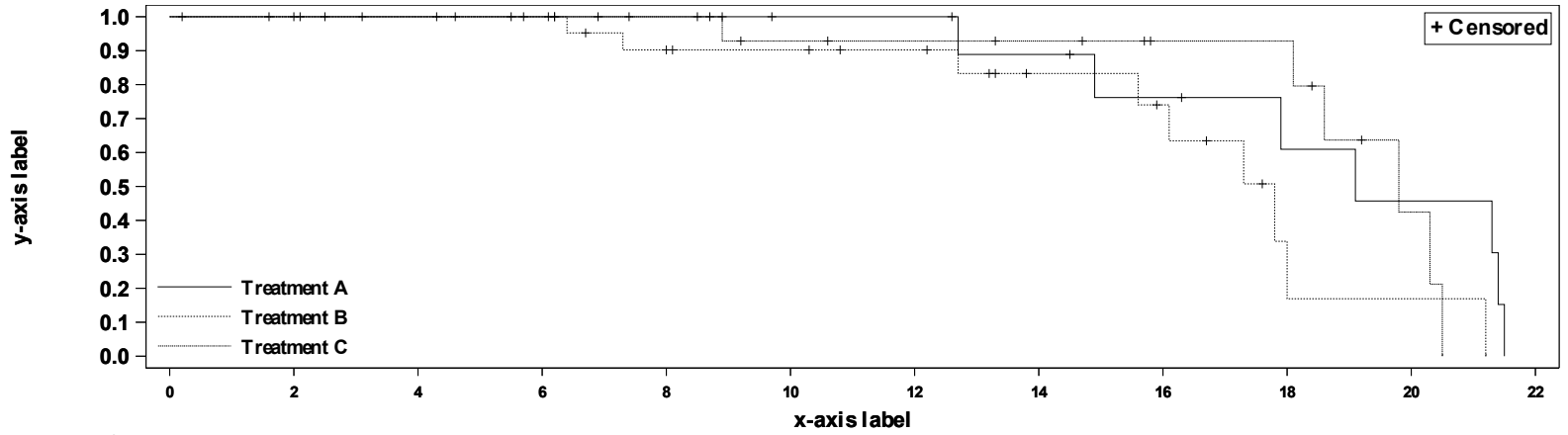
Display the following footnotes:

HR = Hazard Ratio; CI = Confidence Interval; AIDS = Acquired Immunodeficiency Syndrome.
Charlson Comorbidity and pre-baseline Barthel Index as derived using the eCRF data.
Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale).

[a] Hazard Ratio calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and the levels of the randomisation stratification factors, ie, geographical region, and Charlson Comorbidity Index and pre-baseline Barthel index as derived using the eCRF data as covariates, except that for the Charlson Comorbidity Index subgroup analysis, the randomisation stratum of Charlson Comorbidity Index will not be included as a covariate; for the Geographical Region subgroup analysis, the randomisation stratum of Geographical Region will not be included as a covariate; and for the pre-baseline Barthel index subgroup analysis, the randomisation stratum of pre-baseline Barthel index will not be included as a covariate.

**Figure 14.2.2.1 Time to Sustained Hospital Discharge - Kaplan-Meier Plot (Intent-To-Treat Population)**




Number of subjects at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment A | 21 | 20 | 19 | 18 | 14 | 10 | 10 | 8 | 6 | 4 | 3 | 0 |
| Treatment B | 28 | 27 | 24 | 22 | 18 | 16 | 14 | 9 | 7 | 2 | 1 | 0 |
| Treatment C | 15 | 15 | 15 | 14 | 14 | 12 | 11 | 10 | 7 | 7 | 2 | 0 |

Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient
i. discharges from the hospital, and
ii. has no subsequent re-admission

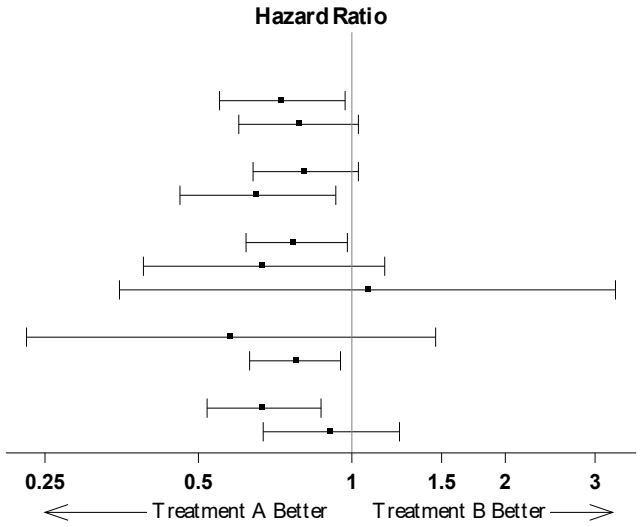
Reference: Table 14.2.2.1.1

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Kaplan-Meier Plot |
| Figure Template ID | FG002 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Time to Sustained Hospital Discharge (days) |
| X-axis Scale | Major tick - 0-42 by 3, Minor tick - Nil |
| Y-axis label | Cumulative Proportion of Sustained Hospital Discharge (1-Cumulative Survival) |
| Y-axis Scale | 0.0 to 1.0 by 0.1 |
| Legend | Line patterns for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear inside plot, bottom right |
| Annotations | Display 'Numbers of patients at risk' at the start of the corresponding day on the x-axis<br>Display censoring symbol legend inside plot, top left |
| Other notes | Parameter option for symbol statement: Interpol = step |

**Figure 14.2.2.2 Time to Sustained Hospital Discharge - Subgroup Analysis - Forest Plot (Intent-To-Treat Population)**

| Subgroup | Treatment A N | Treatment B N | HR (95% CI) |
|---|---|---|---|
| **Age (years)** | | | |
| <65 | 1077 | 1091 | 0.73 (0.55, 0.97) |
| ≥65 | 862 | 846 | 0.79 (0.60, 1.03) |
| **Gender** | | | |
| Male | 1293 | 1245 | 0.81 (0.64, 1.03) |
| Female | 646 | 692 | 0.65 (0.46, 0.93) |
| **Race** | | | |
| White | 1600 | 1619 | 0.77 (0.62, 0.98) |
| Black or African American | 218 | 225 | 0.67 (0.39, 1.16) |
| Other | 88 | 60 | 1.08 (0.35, 3.29) |
| **Ethnicity** | | | |
| Hispanic or Latino | 75 | 72 | 0.58 (0.23, 1.46) |
| Not Hispanic | 1852 | 1857 | 0.78 (0.63, 0.95) |
| **Body Mass Index** | | | |
| < 30 | 1123 | 1096 | 0.67 (0.52, 0.87) |
| ≥ 30 | 810 | 835 | 0.91 (0.67, 1.24) |



*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Forest Plot |
| Figure Template ID | FG006 |
| Treatment display details | Display 2 treatment groups per page. Plitidepsin 2.5mg vs Control Arm on page 1 and Plitidepsin 1.5mg vs Control Arm on page 2. |
| X-axis label | <---------- Control Arm Better Plitidepsin 2.5mg Better ---------> on page 1.<br><---------- Control Arm Better Plitidepsin 1.5mg Better ---------> on page 2. |
| X-axis Scale | 0.33; 0.5; 0.66; 1; 1.5; 2; 3. |
| Y-axis label | Nil. |
| Y-axis Scale | Major tick: Nil>>, Minor tick: Nil. |
| | Display 2 treatment groups per page. |
| | Subgroup Plitidepsin 2.5mg N Control Arm N HR [a] (95% CI) Hazard Ratio (on page 1) |
| Legend | Subgroup Plitidepsin 1.5mg N Control Arm N HR [a] (95% CI) Hazard Ratio (on page 2) |
| Legend position | Top |
| Annotations | Include reference line |
| Other notes | Display subgroups as following: |

All patients
Charlson Comorbidity Index
0 - 1
> 1
Geographical Region
Europe
Rest of the World
Pre-baseline Barthel index
≥ 90
< 90
Patients included before and after amendment
Protocol v.6 or before
Protocol v.7

Display the following footnotes:

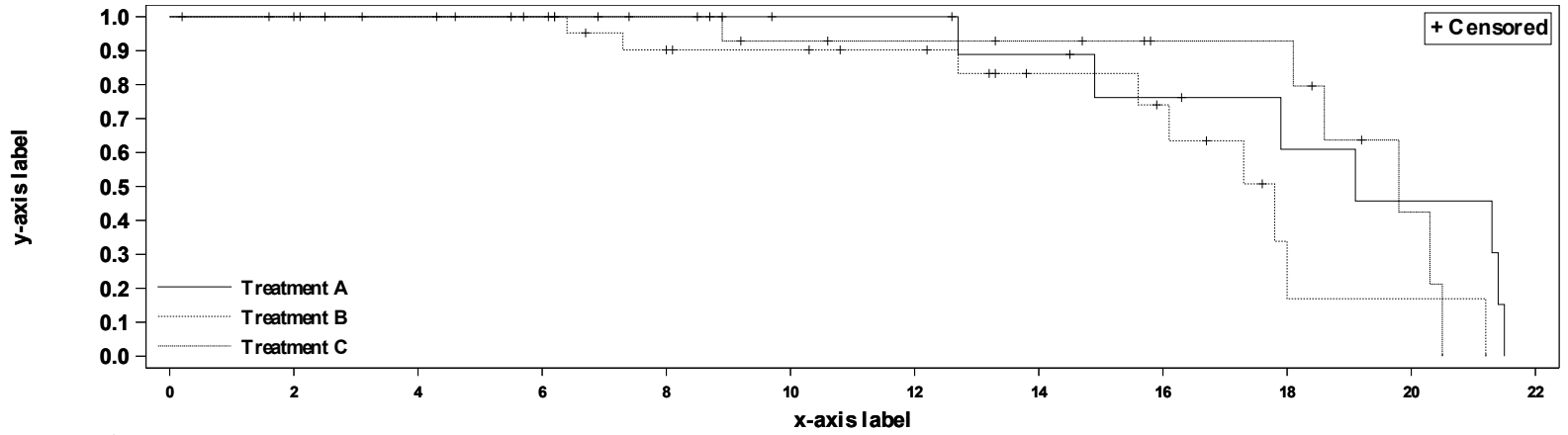
HR = Hazard Ratio; CI = Confidence Interval.
Charlson Comorbidity and pre-baseline Barthel Index as derived using the eCRF data.

Notes: Sustained (ie, with no subsequent readmission to Day 31) hospital discharge (in days), defined as the first day, from randomisation through completion of the study, on which a patient

i. discharges from the hospital, and
ii. has no subsequent re-admission

[a] Hazard Ratio calculated using a Cox proportional-hazards regression model, including the fixed effect of the treatment group and the levels of the randomisation stratification factors, ie, geographical region, and Charlson Comorbidity Index and pre-baseline Barthel index as derived using the eCRF data as covariates, except that for the Charlson Comorbidity Index subgroup analysis, the randomisation stratum of Charlson Comorbidity Index will not be included as a covariate; for the Geographical Region subgroup analysis, the randomisation stratum of Geographical Region will not be included as a covariate; and for the pre-baseline Barthel index subgroup analysis, the randomisation stratum of pre-baseline Barthel index will not be included as a covariate.

**Figure 14.2.2.3 Time to Intensification of Respiratory Support - Kaplan-Meier Plot (Intent-To-Treat Population)**




Number of subjects at risk

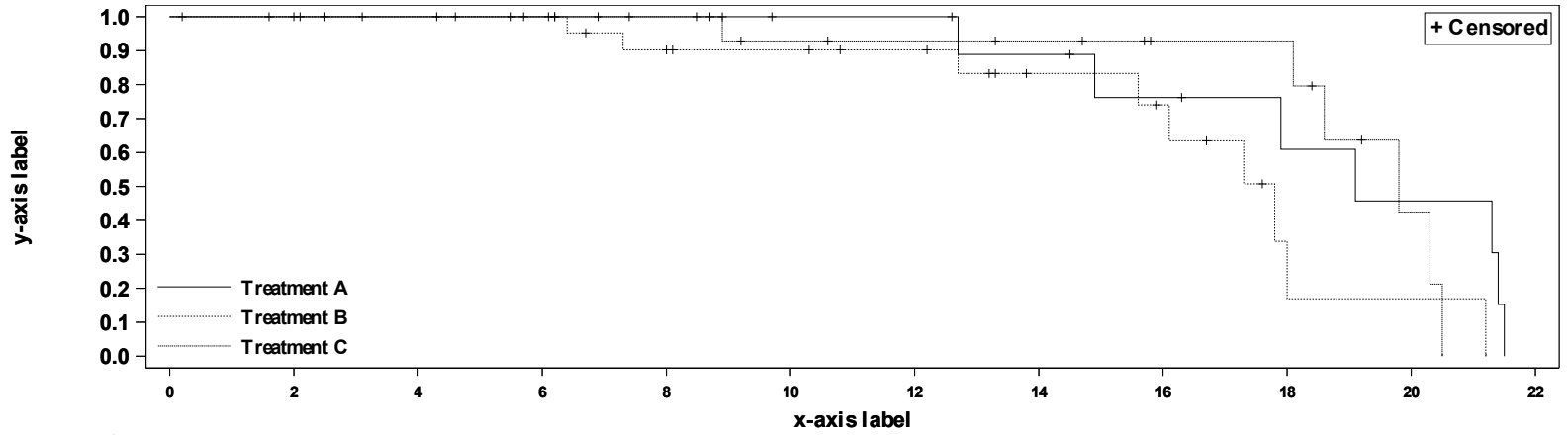
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment A | 21 | 20 | 19 | 18 | 14 | 10 | 10 | 8 | 6 | 4 | 3 | 0 |
| Treatment B | 28 | 27 | 24 | 22 | 18 | 16 | 14 | 9 | 7 | 2 | 1 | 0 |
| Treatment C | 15 | 15 | 15 | 14 | 14 | 12 | 11 | 10 | 7 | 7 | 2 | 0 |

Notes: Time to intensification of respiratory support (in days), defined as the first day, from randomisation through completion of the study, on which a patient satisfies a category > 6 on the 11-point WHO Clinical Progression Scale or dies due to any cause.
Reference: Table 14.2.3.7.1

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Kaplan-Meier Plot |
| Figure Template ID | FG002 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Time to Intensification of Respiratory Support (days) |
| X-axis Scale | Major tick - 0-42 by 3, Minor tick - Nil |
| Y-axis label | Cumulative Survival |
| Y-axis Scale | 0.0 to 1.0 by 0.1 |
| Legend | Line patterns for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear inside plot, bottom right |
| Annotations | Display 'Numbers of patients at risk' at the start of the corresponding day on the x-axis<br>Display censoring symbol legend inside plot, top left |
| Other notes | Parameter option for symbol statement: Interpol = step |

**Figure 14.2.2.4 Time to Initiation with Immune-Modulating Drugs - Kaplan-Meier Plot (Intent-To-Treat Population)**




Number of subjects at risk

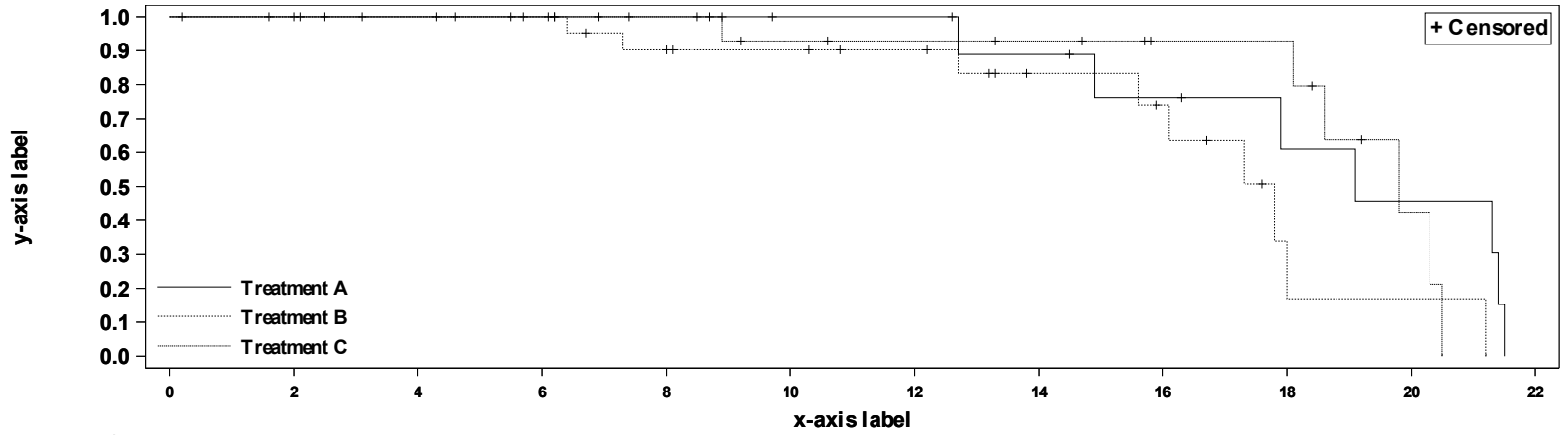
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment A | 21 | 20 | 19 | 18 | 14 | 10 | 10 | 8 | 6 | 4 | 3 | 0 |
| Treatment B | 28 | 27 | 24 | 22 | 18 | 16 | 14 | 9 | 7 | 2 | 1 | 0 |
| Treatment C | 15 | 15 | 15 | 14 | 14 | 12 | 11 | 10 | 7 | 7 | 2 | 0 |

Notes: Time to initiation with immune-modulating drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent immune-modulating drugs.
Reference: Table 14.2.3.12.1

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Kaplan-Meier Plot |
| Figure Template ID | FG002 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Time to Initiation with Immune-Modulating Drugs (days) |
| X-axis Scale | Major tick - 0-42 by 3, Minor tick - Nil |
| Y-axis label | Cumulative Survival |
| Y-axis Scale | 0.0 to 1.0 by 0.1 |
| Legend | Line patterns for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear inside plot, bottom right |
| Annotations | Display 'Numbers of patients at risk' at the start of the corresponding day on the x-axis<br>Display censoring symbol legend inside plot, top left |
| Other notes | Parameter option for symbol statement: Interpol = step |

**Figure 14.2.2.5 Time to Initiation with Antiviral Drugs - Kaplan-Meier Plot (Intent-To-Treat Population)**




Number of subjects at risk

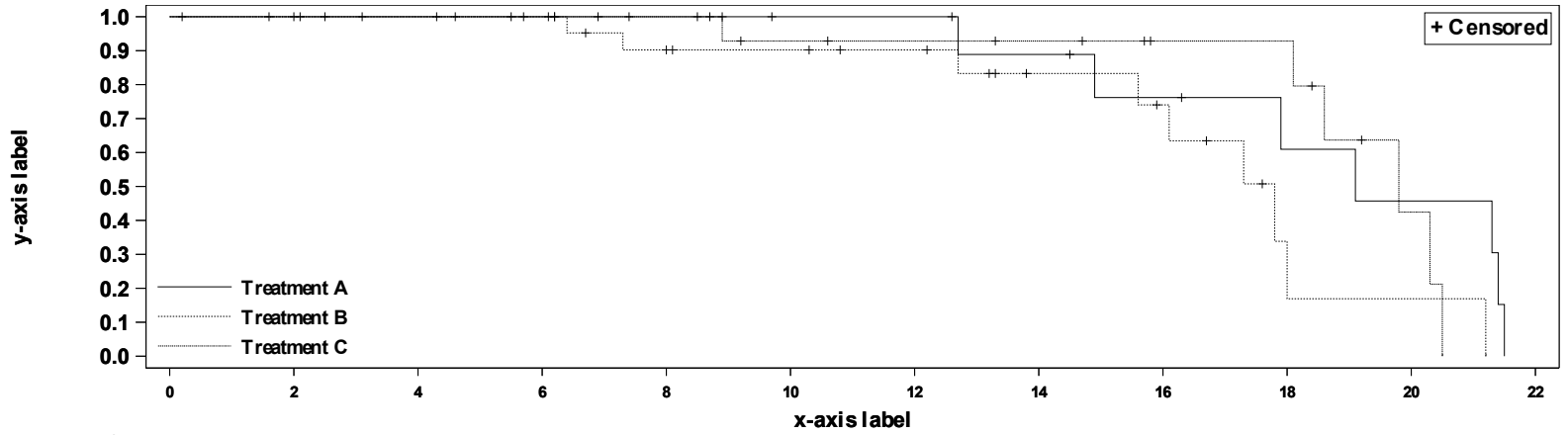
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment A | 21 | 20 | 19 | 18 | 14 | 10 | 10 | 8 | 6 | 4 | 3 | 0 |
| Treatment B | 28 | 27 | 24 | 22 | 18 | 16 | 14 | 9 | 7 | 2 | 1 | 0 |
| Treatment C | 15 | 15 | 15 | 14 | 14 | 12 | 11 | 10 | 7 | 7 | 2 | 0 |

Notes: Time to initiation with antiviral drugs (in days), defined as the first day, from randomisation through completion of the study, on which a patient receives subsequent antiviral drugs.
Reference: Table 14.2.3.13.1

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Kaplan-Meier Plot |
| Figure Template ID | FG002 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Time to Initiation with Antiviral Drugs (days) |
| X-axis Scale | Major tick - 0-42 by 3, Minor tick - Nil |
| Y-axis label | Cumulative Survival |
| Y-axis Scale | 0.0 to 1.0 by 0.1 |
| Legend | Line patterns for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear inside plot, bottom right |
| Annotations | Display 'Numbers of patients at risk' at the start of the corresponding day on the x-axis<br>Display censoring symbol legend inside plot, top left |
| Other notes | Parameter option for symbol statement: Interpol = step |

**Figure 14.2.2.6 Mortality - Kaplan-Meier Plot (Intent-To-Treat Population)**




Number of subjects at risk

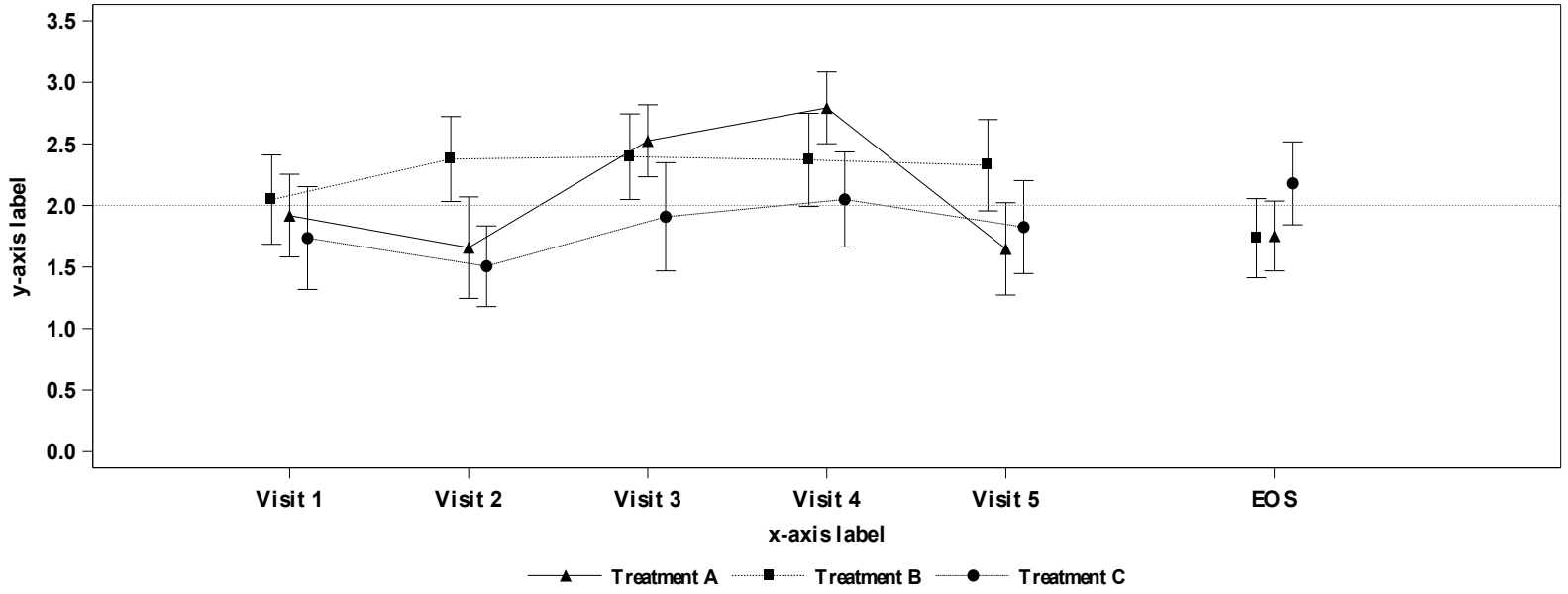
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment A | 21 | 20 | 19 | 18 | 14 | 10 | 10 | 8 | 6 | 4 | 3 | 0 |
| Treatment B | 28 | 27 | 24 | 22 | 18 | 16 | 14 | 9 | 7 | 2 | 1 | 0 |
| Treatment C | 15 | 15 | 15 | 14 | 14 | 12 | 11 | 10 | 7 | 7 | 2 | 0 |

Reference: Table 14.2.3.12

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Kaplan-Meier Plot |
| Figure Template ID | FG002 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Time to Death (days) |
| X-axis Scale | Major tick - 0-42 by 3, Minor tick - Nil |
| Y-axis label | Cumulative Survival |
| Y-axis Scale | 0.0 to 1.0 by 0.1 |
| Legend | Line patterns for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear inside plot, bottom right |
| Annotations | Display 'Numbers of patients at risk' at the start of the corresponding day on the x-axis<br>Display censoring symbol legend inside plot, top left |
| Other notes | Parameter option for symbol statement: Interpol = step |

**Figure 14.2.2.7 SARS-CoV-2 viral load ($log_{10}$ copies/mL) by Visit, (Median [Q1-Q3]) by Treatment Group (Full Analysis Set)**

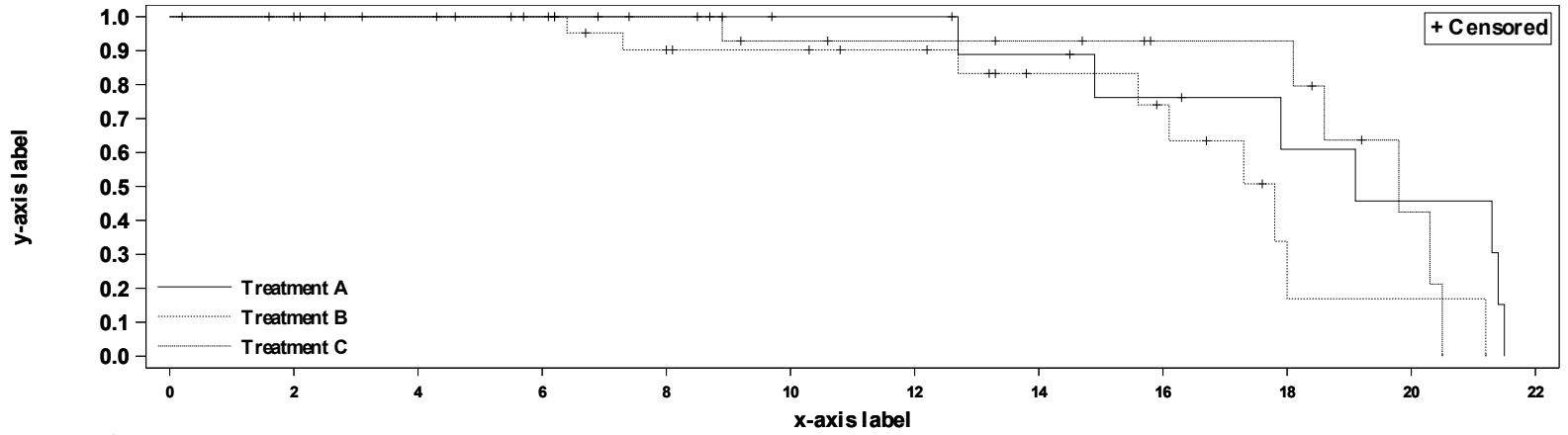



Reference: Table 14.2.3.18

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Median (Q1-Q3) Plot |
| Figure Template ID | FG003 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Visit |
| X-axis Scale | Major tick - Day 1 and Day 8, Minor tick - Nil |
| Y-axis label | Median (Q1-Q3) |
| Y-axis Scale | 0.0 to 10.0 by 1 |
| Legend | Line with symbols for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear below x-axis, centered |
| Annotations | None |
| Other notes | Parameter option for symbol statement: Interpol = join |

**Figure 14.2.2.8 Time to Sustained Withdrawal of Oxygen Supplementation - Kaplan-Meier Plot - Pooled Plitidepsin Arms (Intent-To-Treat Population)**




Number of subjects at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment A | 21 | 20 | 19 | 18 | 14 | 10 | 10 | 8 | 6 | 4 | 3 | 0 |
| Treatment B | 28 | 27 | 24 | 22 | 18 | 16 | 14 | 9 | 7 | 2 | 1 | 0 |
| Treatment C | 15 | 15 | 15 | 14 | 14 | 12 | 11 | 10 | 7 | 7 | 2 | 0 |

Notes: Sustained withdrawal of oxygen supplementation (in days) with no subsequent reutilisation during remaining study period is defined as the first day, from randomisation through completion of the study, on which a patient

i. satisfies categories 0 to 4 on the 11-point WHO Clinical Progression Scale, and
ii. has no subsequent reutilisation of oxygen supplementation (5 to 10 on the 11-point WHO Clinical Progression Scale)

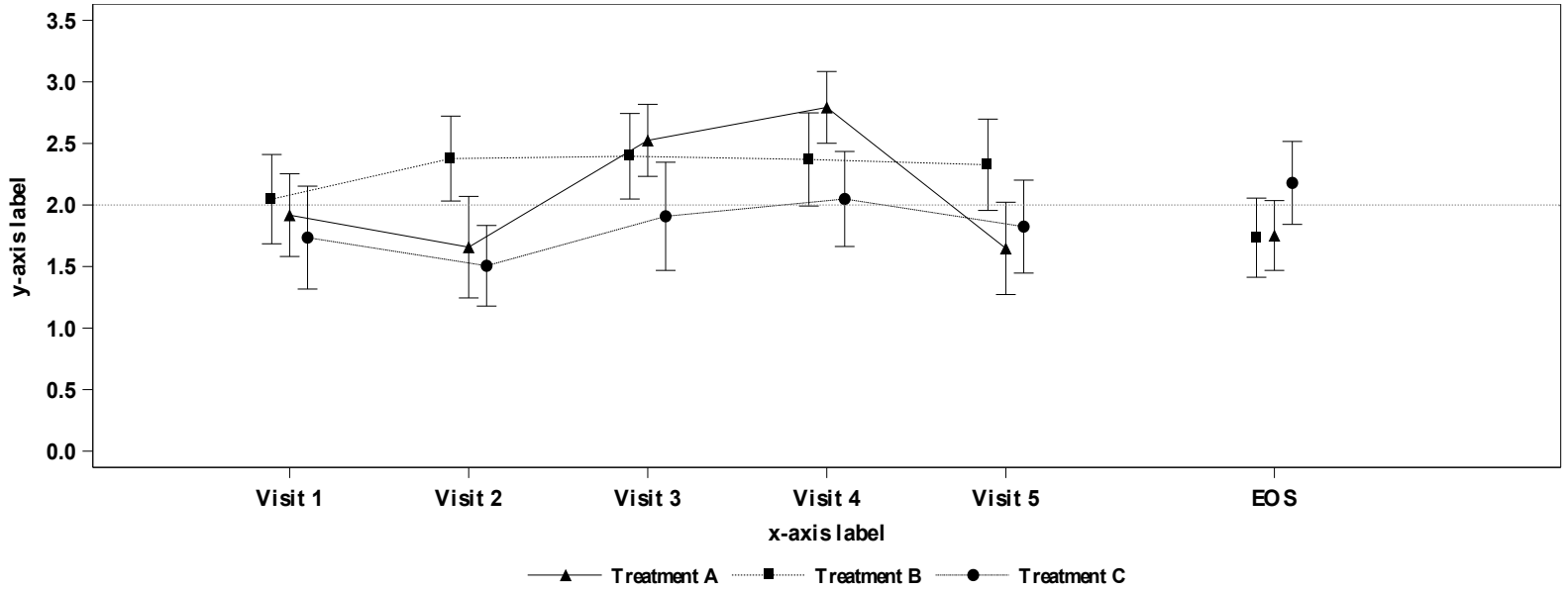
Reference: Table 14.2.1.1.1

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Kaplan-Meier Plot |
| Figure Template ID | FG002 |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Time to Sustained Withdrawal of Oxygen Supplementation (days) |
| X-axis Scale | Major tick - 0-42 by 3, Minor tick - Nil |
| Y-axis label | Cumulative Proportion of Sustained Withdrawal of Oxygen Supplementation (1-Cumulative Survival) |
| Y-axis Scale | 0.0 to 1.0 by 0.1 |
| Legend | Line patterns for Pooled Plitidepsin Arms, Control Arm |
| Legend position | Appear inside plot, bottom right |
| Annotations | Display 'Numbers of patients at risk' at the start of the corresponding day on the x-axis<br>Display censoring symbol legend inside plot, top left |
| Other notes | Parameter option for symbol statement: Interpol = step |

**Figure 14.2.2.9.1 Proinflammatory Biomarkers over time (Median [Q1, Q3]) by Treatment Group (Full Analysis Set)**

Parameter: Parameter (unit)



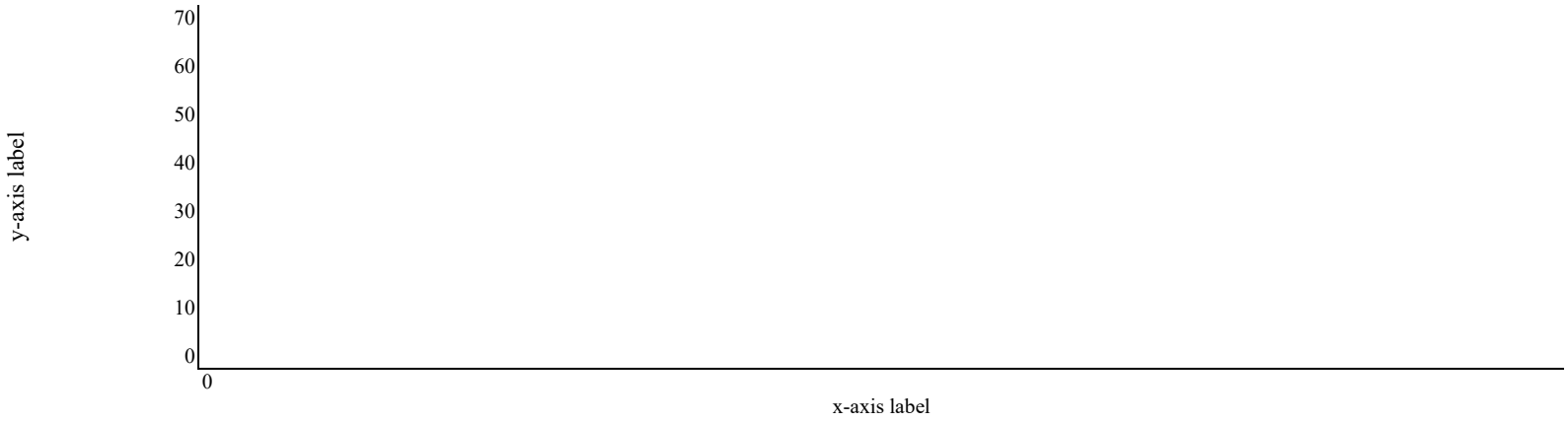

Reference: Table 14.2.3.20

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Median (Q1-Q3) Plot |
| Figure Template ID | FG003<br>Parameters are: CRP (mg/L) referred to ULN, ferritin (ug/L) referred to ULN, IL-1β (pg/mL), IL-6 (pg/mL), IL-10 (pg/mL), and TNFα (pg/mL) |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Visit |
| X-axis Scale | Major tick - Baseline, Day 2, Day 3, Day 4, Day 8, and Day 31, Minor tick - Nil |
| Y-axis label | Median (Q1-Q3) |
| Y-axis Scale | Adapt per parameter |
| Legend | Line with symbols for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear below x-axis, centered |
| Annotations | None |
| Other notes | Parameter option for symbol statement: Interpol = join |

**Figure 14.2.2.9.2 Proinflammatory Biomarkers over time - Spaghetti plot (Full Analysis Set)**

Parameter: Parameter (unit)
Treatment Group: <<Plitidepsin 2.5mg (N = XXX)/Plitidepsin 1.5mg (N = XXX)/Control Arm (N = XXX)>>



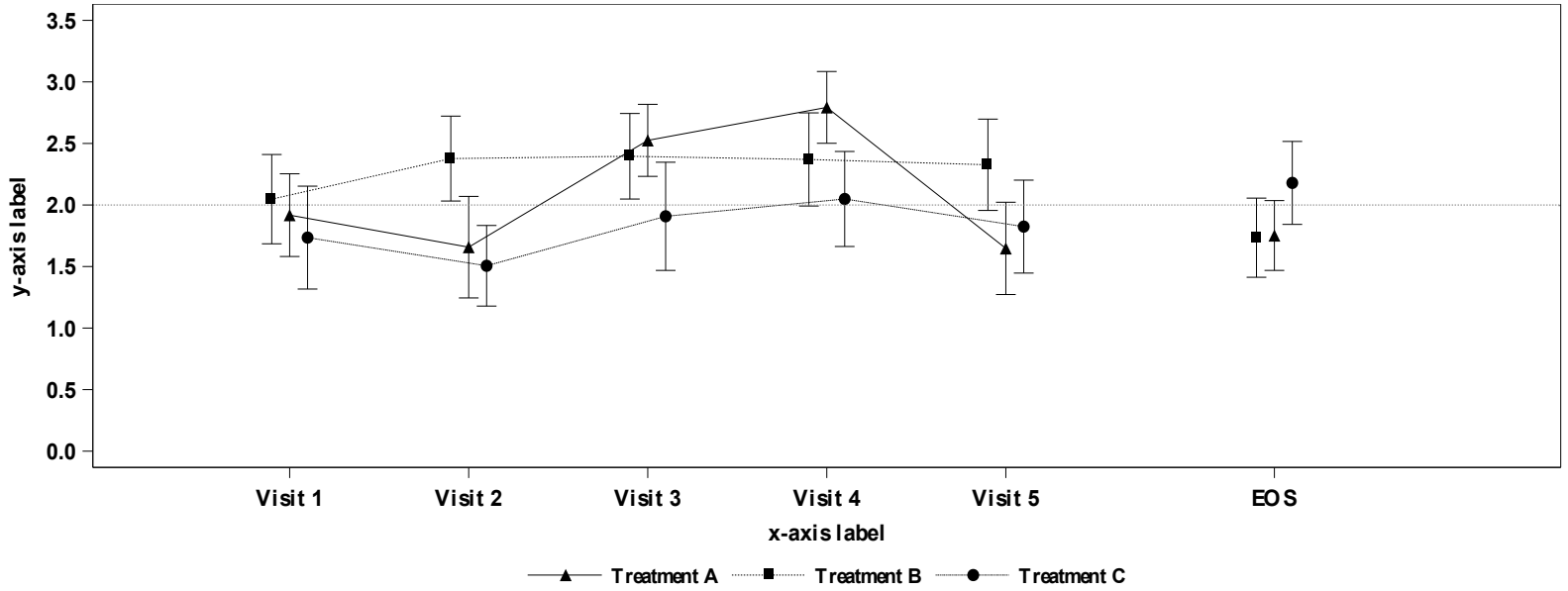

N = number of patients in analysis set.
Reference: Listing 16.2.8.1.3

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Spaghetti plot |
| Figure Template ID | FG010 |
| Treatment display details | Parameters are: CRP (mg/L) referred to ULN, ferritin (ug/L) referred to ULN, IL-1β (pg/mL), IL-6 (pg/mL), IL-10 (pg/mL), and TNFα (pg/mL)<br>Use solid lines for all individual profiles<br>Use a thicker solid line to represent the median values |
| X-axis label | Visit |
| X-axis Scale | Major tick - Baseline, Day 2, Day 3, Day 4, Day 8, and Day 31, Minor tick - Nil |
| Y-axis label | Parameter (units) |
| Y-axis Scale | Adapt per parameter |
| Legend | Line with symbols for median values |
| Legend position | Appear below x-axis, centered |
| Annotations | None |
| Other notes | Display a line for the median values |

**Figure 14.3.4.1.1 Laboratory Results over time (Median [Q1, Q3]) by Treatment Group (As Treated Population)**

Parameter: Parameter (unit)



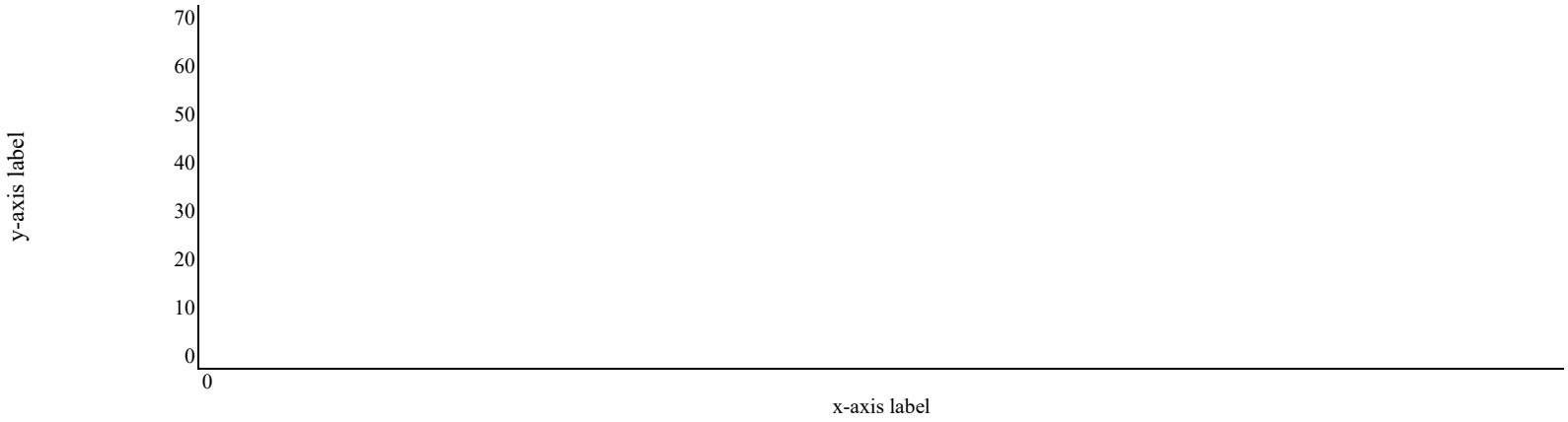

Reference: Tables 14.3.4.1 and 14.3.4.2.

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Median (Q1-Q3) Plot |
| Figure Template ID | FG003<br>Parameters are: Lymphocytes (Gl/L), NLR (neutrophils/lymphocytes ratio), ALT (U/L), CPK (U/L), Troponin T (ng/L), NT-ProBNP (pmol/L), and Procalcitonin (ng/mL) |
| Treatment display details | For line and symbols, follow Section 2.12 Graphical Presentations |
| X-axis label | Visit |
| X-axis Scale | Major tick - Baseline, Day 2, Day 3, Day 4, Day 8, and Day 31, Minor tick - Nil |
| Y-axis label | Median (Q1-Q3) |
| Y-axis Scale | Adapt per parameter |
| Legend | Line with symbols for Plitidepsin 2.5mg, Plitidepsin 1.5mg, Control Arm |
| Legend position | Appear below x-axis, centered |
| Annotations | None |
| Other notes | Parameter option for symbol statement: Interpol = join |

**Figure 14.3.4.1.2 Laboratory Results over time - Spaghetti plot (As Treated Population)**

Parameter: Parameter (unit)
Treatment Group: <<Plitidepsin 2.5mg (N = XXX)/Plitidepsin 1.5mg (N = XXX)/Control Arm (N = XXX)>>




N = number of patients in analysis set.
Reference: Listings 16.2.8.1.1 and 16.2.8.1.2

*Programming notes (not part of the figure):*

| | |
|---|---|
| Type of figure | Spaghetti plot |
| Figure Template ID | FG010 |
| Treatment display details | Parameters are: Lymphocytes (Gl/L), NLR (neutrophils/lymphocytes ratio), ALT (U/L), CPK (U/L), Troponin T (ng/L), NT-ProBNP (pmol/L), and Procalcitonin (ng/mL)<br>Use solid lines for all individual profiles<br>Use a thicker solid line to represent the median values |
| X-axis label | Visit |
| X-axis Scale | Major tick - Baseline, Day 2, Day 3, Day 4, Day 8, and Day 31, Minor tick - Nil |
| Y-axis label | Parameter (units) |
| Y-axis Scale | Adapt per parameter |
| Legend | Line with symbols for median values |
| Legend position | Appear below x-axis, centered |
| Annotations | None |
| Other notes | Display a line for the median values |

# 6. APPENDIX 1. LABORATORY TESTS – PRECISION LEVELS

| Category | Analyte | SI Unit | Precision (Decimal Point) |
|---|---|---|---|
| Haematology | RBC Count | Tl/L | 1 |
| Haematology | Haemoglobin | g/L | 0 |
| Haematology | Haematocrit | 1 | 3 |
| Haematology | WBC Count | G/L | 1 |
| Haematology | Neutrophils | % | 1 |
| Haematology | Abs. Neutrophils | Gl/L | 2 |
| Haematology | Eosinophils | % | 1 |
| Haematology | Abs. Eosinophils | Gl/L | 2 |
| Haematology | Basophils | % | 1 |
| Haematology | Abs. Basophils | Gl/L | 2 |
| Haematology | Lymphocytes | % | 1 |
| Haematology | Abs. Lymphocytes | Gl/L | 2 |
| Haematology | Monocytes | % | 1 |
| Haematology | Abs. Monocytes | Gl/L | 2 |
| Haematology | Platelet count | Gl/L | 0 |
| Chemistry | ALT(SGPT) | U/L | 0 |
| Chemistry | AST(SGOT) | U/L | 0 |
| Chemistry | Alkaline Phosphatase (ALP) | U/L | 0 |
| Chemistry | GGT | U/L | 0 |
| Chemistry | LDH | U/L | 0 |
| Chemistry | Total Bilirubin | umol/L | 1 |
| Chemistry | Direct Bilirubin | umol/L | 1 |
| Chemistry | Glucose | mmol/L | 1 |
| Chemistry | Sodium | mmol/L | 1 |
| Chemistry | Potassium | mmol/L | 1 |
| Chemistry | Calcium (adjusted) | mmol/L | 2 |
| Chemistry | Magnesium | mmol/L | 3 |
| Chemistry | Creatinine | umol/L | 1 |
| Chemistry | Calculated Creatinine Clearance | mL/sec | 1 |
| Chemistry | Albumin | g/L | 0 |

| Category | Analyte | SI Unit | Precision (Decimal Point) |
|---|---|---|---|
| Chemistry | Creatine Phosphokinase (CPK) | U/L | 0 |
| Chemistry | Troponin T | ng/L | 2 |
| Chemistry | NT-pro BNP | pmol/L | 2 |
| Chemistry | Blood Urea Nitrogen | mmol/L | 1 |
| Chemistry | Amylase | U/L | 0 |
| Chemistry | Lipase | U/L | 0 |
| Chemistry | Procalcitonin | ng/mL | 3 |
| Immunology | CRP | mg/L | 1 |
| Immunology | Ferritin | ug/L | 1 |
| Immunology | IL-1β | pg/mL | 2 |
| Immunology | IL-6 | pg/mL | 2 |
| Immunology | IL-10 | pg/mL | 2 |
| Immunology | TNFα | pg/mL | 2 |
| Coagulation | D-dimer | mg/L | 3 |

### 16.1.9.2. Quality Tolerance Limit Definitions

| Quality Tolerance Limit Definition | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Definition** | **The table shown below is copy paste of what was approved.** | **Unit** | **Tolerance Limit <s>** | **Justification for Tolerance Limit** | **Secondary Limit <s>** | **How will data be collected, tracked and reviewed (*include data source and system/tool(s) used for tracking)*** | **Role responsible for tracking** | **QTL Modified Y/N** | **Modification Justification** |
| Proportion (%) of randomized and treated subjects not meeting inclusion/exclu sio n criteria | Proportion (%) of randomized and treated subjects (i.e. subjects that have signed an Informed Consent, have a randomization date and have taken at least 1 dose of the study treatment in EDC) with deviation of at least one inclusion/exclusion criteria (i.e. patients with IPD noted in PD subcategory Inclusion/Exclusion Criteria in RIM)<br><br>Defined as "(Number of randomized and treated subjects with deviation of at least one inclusion or exclusion criteria/reference number)*100".<br><br>Where reference number will be based on the protocol sample size (i.e. 609 patients) until 80% of the subjects are randomized (487 subjects) or current number of randomized subjects after 80% of the subjects are randomized. | A high number of subjects not meeting the entrance criteria can have a negative impact on interpretation of the primary endpoint and overall validity of the trial results. | % | 2.0% | The number of patients included by mistake should be the lowest possible. | 1% | Subjects with Important Protocol Deviations for inc/exc criteria in RIM. Monthly review with export of protocol deviations. | Project Leader | Proportion (%) of randomized and treated subjects not meeting inclusion/exclu sion criteria | Proportion (%) of randomized and treated subjects (i.e. subjects that have signed an Informed Consent, have a randomization date and have taken at least 1 dose of the study treatment in EDC) with deviation of at least one inclusion/exclusion criteria (i.e. patients with IPD noted in PD subcategory Inclusion/Exclusion Criteria in RIM)<br><br>Defined as "(Number of randomized and treated subjects with deviation of at least one inclusion or exclusion criteria/reference number)*100".<br><br>Where reference number will be based on the protocol sample size (i.e. 609 patients) until 80% of the subjects are randomized (487 subjects) or current number of randomized subjects after 80% of the subjects are randomized. |

| Quality Tolerance Limit Definition | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Definition** | **The table shown below is copy paste of what was approved.** | **Unit** | **Tolerance Limit <s>** | **Justification for Tolerance Limit** | **Secondary Limit <s>** | **How will data be collected, tracked and reviewed (*include data source and system/tool(s) used for tracking)*** | **Role responsible for tracking** | **QTL Modified Y/N** | **Modification Justification** |
| Proportion (%) subjects with premature study treatment discontinuation | Proportion (%) of randomized and treated subjects (i.e. subjects that have signed an Informed Consent, have a randomization date and have taken at least 1 dose of the study treatment in EDC) who discontinued the study treatment prematurely (i.e. subjects with Premature Discontinuation of Study Treatment collected in EDC).<br><br>Defined as "(Number of randomized and treated subjects who discontinued the study treatment prematurely/reference number)*100".<br><br>Where reference number will be based on the protocol sample size (i.e. 609 patients) until 80% of the subjects are randomized (487 subjects) or current number of randomized subjects after 80% of the subjects are randomized. | Premature drug discontinuation rate is<br>the key factor limiting exposure to studied treatments in the setting. Decreased exposure decreases the power of the trial. | % | 10.0% | It may start impacting final data analysis and results. | 5.0% | Subjects with Premature Discontinuation of Study Treatment collected in EDC. Monthly review | Project Leader | Proportion (%) subjects with premature study treatment discontinuation | Proportion (%) of randomized and treated subjects (i.e. subjects that have signed an Informed Consent, have a randomization date and have taken at least 1 dose of the study treatment in EDC) who discontinued the study treatment prematurely (i.e. subjects with Premature Discontinuation of Study Treatment collected in EDC).<br><br>Defined as "(Number of randomized and treated subjects who discontinued the study treatment prematurely/reference number)*100".<br><br>Where reference number will be based on the protocol sample size (i.e. 609 patients) until 80% of the subjects are randomized (487 subjects) or current number of randomized subjects after 80% of the subjects are randomized. |

| Quality Tolerance Limit Definition | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Definition** | **The table shown below is copy paste of what was approved.** | **Unit** | **Tolerance Limit <s>** | **Justification for Tolerance Limit** | **Secondary Limit <s>** | **How will data be collected, tracked and reviewed (*include data source and system/tool(s) used for tracking)*** | **Role responsible for tracking** | **QTL Modified Y/N** | **Modification Justification** |
| Proportion (%) of subjects lost to follow-up in study | Proportion (%) of randomized and treated subjects (i.e. subjects that have signed an Informed Consent, have a randomization date and have taken at least 1 dose of the study treatment in EDC) who have no status documented by the site at the end of the study (i.e. patients with Study Termination collected as Lost to Follow-up in EDC).<br><br>Defined as "(Number of randomized and treated subjects who have no status documented by the site at the end of the study/reference number)*100".<br><br>Where reference number will be based on the protocol sample size (i.e. 609 patients) until 80% of the subjects are randomized (487 subjects) or current number of randomized subjects after 80% of the subjects are randomized. | A high number of subjects lost to follow-up can have a negative impact on interpretation of primary endpoint. | % | 8% | It may start impacting final data analysis and results. | 5% | Subjects with Study Termination collected as Lost to Follow-up in EDC. Monthly review | Project Leader | Proportion (%) of subjects lost to follow-up in study | Proportion (%) of randomized and treated subjects (i.e. subjects that have signed an Informed Consent, have a randomization date and have taken at least 1 dose of the study treatment in EDC) who have no status documented by the site at the end of the study (i.e. patients with Study Termination collected as Lost to Follow-up in EDC).<br><br>Defined as "(Number of randomized and treated subjects who have no status documented by the site at the end of the study/reference number)*100".<br><br>Where reference number will be based on the protocol sample size (i.e. 609 patients) until 80% of the subjects are randomized (487 subjects) or current number of randomized subjects after 80% of the subjects are randomized. |