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

Summary

EudraCT number	2022-002489-34
Trial protocol	ES HU PT PL IT BE FR
Global end of trial date	19 April 2024

Results information

Result version number	v1 (current)
This version publication date	31 October 2024
First version publication date	31 October 2024

Trial information

Trial identification

Sponsor protocol code	AV-APL-B-002-22

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05705167
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar, S.A.
Sponsor organisation address	Avda. de los Reyes, 1, Polígono Industrial “La Mina”, Colmenar Viejo (Madrid), Spain, 28770
Public contact	Clinical Development, Department of PharmaMar´s Oncology., Business Unit., Pharma Mar, S.A., +34 918466000, clinicaltrials@pharmamar.com
Scientific contact	Clinical Development, Department of PharmaMar´s Oncology., Business Unit., Pharma Mar, S.A., +34 918466000, clinicaltrials@pharmamar.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to evaluate the efficacy of plitidepsin in pre-specified groups of immunocompromised participants with symptomatic COVID-19 requiring hospital care versus control in terms of mortality.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice, including the archiving of essential documents. An independent data monitoring committee was established to provide study oversight considering that this was a multicentre, randomised study being performed in a population at high risk for morbidity and mortality.

Background therapy:

Best standard care as per applicable local, institutional, national, supranational COVID-19 treatment guidelines.

Evidence for comparator:

Other regulatory-approved antiviral (if clinically indicated) were administered to participants in control groups.

Actual start date of recruitment	30 December 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Portugal: 4
Worldwide total number of subjects	37
EEA total number of subjects	37

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	25
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 37 participants were enrolled at 15 investigative sites between April 2023 and April 2024. Randomised participants who received at least 1 dose of study treatment and completed follow-up for survival until Day 30 (±2) were included in the Full Analysis Set (FAS) population.

Pre-assignment

Screening details:

Disposition data pertaining to the participants not included in the FAS Population are presented within the pre-assignment period due to EudraCT system limitations.

Pre-assignment period milestones

Number of subjects started	37
Number of subjects completed	25

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomised but not Treated: 9
Reason: Number of subjects	Discontinued Prior to FAS Eligibility: 3

Period 1

Period 1 title	Overall Study - FAS Population (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1: Plitidepsin 2.5 mg

Arm description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute intravenous (IV) infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Arm type	Experimental
Investigational medicinal product name	Plitidepsin
Investigational medicinal product code	SAPL01
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion over 60-minutes.

Arm title	Group 1: Control

Arm description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Arm type	Other regulatory-approved antiviral

No investigational medicinal product assigned in this arm	
Arm title	Group 2: Plitidepsin 2.5 mg

Arm description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Arm type	Experimental
Investigational medicinal product name	Plitidepsin
Investigational medicinal product code	SAPL01
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion over 60-minutes.

Arm title	Group 2: Control

Arm description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Arm type	Other regulatory-approved antiviral
No investigational medicinal product assigned in this arm	
Arm title	Group 3: Plitidepsin 2.5 mg

Arm description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Arm type	Experimental
Investigational medicinal product name	Plitidepsin
Investigational medicinal product code	SAPL01
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion over 60-minutes.

Arm title	Group 3: Control

Arm description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Arm type	Other regulatory-approved antiviral
No investigational medicinal product assigned in this arm	
Arm title	Group 4: Plitidepsin 2.5 mg

Arm description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 4.

Group 4 – Other situations with immune deficiencies.

Arm type	Experimental
Investigational medicinal product name	Plitidepsin
Investigational medicinal product code	SAPL01
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion over 60-minutes.

Number of subjects in period 1[1]	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg
Started	2	1	10
Completed	2	1	7
Not completed	0	0	3
Death	-	-	3

Number of subjects in period 1[1]	Group 2: Control	Group 3: Plitidepsin 2.5 mg	Group 3: Control
Started	3	1	1
Completed	3	0	0
Not completed	0	1	1
Death	-	1	1

Number of subjects in period 1[1]	Group 4: Plitidepsin 2.5 mg
Started	7
Completed	6
Not completed	1
Death	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Disposition data pertaining to the participants not included in the FAS Population are presented within the pre-assignment period due to EudraCT system limitations.

Baseline characteristics

Reporting groups

Reporting group title	Group 1: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute intravenous (IV) infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Reporting group title	Group 1: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Reporting group title	Group 2: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Reporting group title	Group 2: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Reporting group title	Group 3: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Reporting group title	Group 3: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Reporting group title	Group 4: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 4.

Group 4 – Other situations with immune deficiencies.

Reporting group values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg
Number of subjects	2	1	10
Age categorical Units: Subjects			
< 65 years	1	0	3
≥ 65 years - < 75 years	1	1	6
≥ 75 years	0	0	1
Gender categorical Units: Subjects			
Female	1	1	5
Male	1	0	5
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	2	1	10
Other	0	0	0

Reporting group values	Group 2: Control	Group 3: Plitidepsin 2.5 mg	Group 3: Control
Number of subjects	3	1	1
Age categorical Units: Subjects			
< 65 years	1	0	0
≥ 65 years - < 75 years	2	0	1
≥ 75 years	0	1	0
Gender categorical Units: Subjects			
Female	2	0	0
Male	1	1	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	3	1	1
Other	0	0	0

Reporting group values	Group 4: Plitidepsin 2.5 mg	Total	
Number of subjects	7	25	
Age categorical Units: Subjects			
< 65 years	1	6	
≥ 65 years - < 75 years	1	12	
≥ 75 years	5	7	

Gender categorical Units: Subjects			
Female	5	14	
Male	2	11	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black	0	0	
Native Hawaiian or other Pacific Islander	1	1	
White	5	23	
Other	1	1	

End points

End points reporting groups

Reporting group title	Group 1: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute intravenous (IV) infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Reporting group title	Group 1: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Reporting group title	Group 2: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Reporting group title	Group 2: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Reporting group title	Group 3: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Reporting group title	Group 3: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Reporting group title	Group 4: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 4.

Group 4 – Other situations with immune deficiencies.

Primary: One-month All-cause Mortality Rate

End point title	One-month All-cause Mortality Rate[1]

End point description:

In the event of the participant initiating another non-protocol therapy, 1-month all-cause mortality rate was evaluated regardless of initiation of new non-protocol therapy.

FAS Population: All randomised participants who received at least 1 dose of study treatment (plitidepsin or control) and completed follow-up for survival until Day 30 (±2). Participants who died before the end of the follow-up period were also included in the FAS population.

End point type	Primary

End point timeframe:

Day 1 to Day 30 (±2)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Additional statistical analysis pre-specified for the primary endpoint could not be entered as we are unable to add "N/A" values within the system due to system limitations.

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	10	3
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 84.2)	0.0 (0.0 to 97.5)	20.0 (2.5 to 55.6)	0.0 (0.0 to 70.8)

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	7	
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 97.5)	100.0 (2.5 to 100.0)	14.3 (0.4 to 57.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Confirmed Negativisation in SARS-CoV-2 Antigen Test or Real Time Polymerase Chain Reaction (RT-PCR) Cycle Threshold (Ct) > 30

End point title	Time to Confirmed Negativisation in SARS-CoV-2 Antigen Test or Real Time Polymerase Chain Reaction (RT-PCR) Cycle Threshold (Ct) > 30

End point description:

Time to confirmed negativisation in SARS-CoV antigen test or RT-PCR Ct>30 was calculated as time from randomisation to the corresponding event using Kaplan-Meier (KM) estimates. Participants with no available data for any time to event efficacy endpoint were censored at time 0, end of study (Day 60 ±3), or date of early study termination. Also, participants who had not achieved the time to event endpoint were censored at the last valid assessment.

FAS Population: All randomised participants who received at least 1 dose of study treatment (plitidepsin

or control) and completed follow-up for survival until Day 30 (±2). Participants who died before the end of the follow-up period were also included in the FAS population. Values of "-99999" and "99999" indicate median and/or confidence intervals (CI) were not reached due to low number of events.

End point type	Secondary

End point timeframe:

Day 1 to Day 60 (±3)

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	10	3
Units: days				
median (confidence interval 95%)	61.0 (-99999 to 99999)	2.0 (-99999 to 99999)	14.0 (2.0 to 99999)	14.0 (4.0 to 99999)

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	7	
Units: days				
median (confidence interval 95%)	13.0 (-99999 to 99999)	10.0 (-99999 to 99999)	14.0 (3.0 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Sustained End of COVID-related Hospital Care

End point title	Time to Sustained End of COVID-related Hospital Care

End point description:

Time to sustained end of COVID-related hospital care from the time of randomisation was calculated as time from randomisation to the corresponding event using KM estimates. Participants with no available data for any time to event efficacy endpoint were censored at time 0, end of study (Day 60 ±3), or date of early study termination. Also, participants who had not achieved the time to event endpoint were censored at the last valid assessment.

FAS Population: All randomised participants who received at least 1 dose of study treatment (plitidepsin or control) and completed follow-up for survival until Day 30 (±2). Participants who died before the end of the follow-up period were also included in the FAS population. Values of "-99999" and "99999" indicate median and/or CI were not reached due to low number of events.

End point type	Secondary

End point timeframe:

Day 1 to Day 60 (±3)

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	10	3
Units: days				
median (confidence interval 95%)	20.5 (2.0 to 99999)	4.0 (-99999 to 99999)	4.5 (2.0 to 99999)	37.0 (13.0 to 99999)

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	7	
Units: days				
median (confidence interval 95%)	24.0 (-99999 to 99999)	2.0 (-99999 to 99999)	7.0 (3.0 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Sustained Improvement and Resolution of Selected COVID-19 Signs/Symptoms

End point title	Time to Sustained Improvement and Resolution of Selected COVID-19 Signs/Symptoms

End point description:

Time to sustained improvement and resolution of all targeted COVID-19 signs/symptoms was calculated as time from randomisation to the corresponding event using KM estimates. Corresponding events were defined as the event occurring on the first of 4 consecutive days when all symptoms scored as National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v5.0; category of moderate-severe intensity, or requiring medical intervention, or limiting instrumental activity of daily living are scored as mild or absent AND all symptoms scored mild or 0 (absent) at study entry are scored as 0. Participants with no available data for any time to event efficacy endpoint were censored at time 0, end of study (Day 60 ±3), or date of early study termination. Also, participants who had not achieved the time to event endpoint were censored at the last valid assessment. Values of "-99999" and "99999" indicate median and/or CI were not reached due to low number of events.

End point type	Secondary

End point timeframe:

Day 1 to Day 60 (±3)

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[2]	1[3]	10[4]	3[5]
Units: days				
median (confidence interval 95%)	99999 (5.0 to 99999)	99999 (-99999 to 99999)	99999 (3.0 to 99999)	14.0 (4.0 to 99999)

Notes:

[2] - FAS Population.

[3] - FAS Population.

[4] - FAS Population.

[5] - FAS Population.

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1[6]	1[7]	7[8]	
Units: days				
median (confidence interval 95%)	17.0 (-99999 to 99999)	2.0 (-99999 to 99999)	37.0 (2.0 to 99999)	

Notes:

[6] - FAS Population.

[7] - FAS Population.

[8] - FAS Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants in Each Category of the World Health Organization (WHO) Clinical Progression Scale (CPS)

End point title	Number of Participants in Each Category of the World Health Organization (WHO) Clinical Progression Scale (CPS)

End point description:

Distribution of participants according to their clinical status by the 11-category WHO CPS:
- Uninfected; no viral ribonucleic acid (RNA) detected
- Asymptomatic; viral RNA detected
- Symptomatic; independent
- Symptomatic; assistance needed
- Hospitalised; no oxygen therapy
- Hospitalised; oxygen by mask or nasal prongs (NP)
- Hospitalised; oxygen by non-invasive ventilation (NIV) or high flow
- Intubation and mechanical ventilation (MV)
- MV or vasopressors
- MV and vasopressors, dialysis, or extracorporeal membrane oxygenation (ECMO) OR
- Death.

FAS Population: All randomised participants who received at least 1 dose of study treatment (plitidepsin or control) and completed follow-up for survival until Day 30 (±2). Participants who died before the end of the follow-up period were also included in the FAS population. Values of "9999" indicate no participants were analysed at that timepoint.

End point type	Secondary

End point timeframe:

Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3)

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	10[9]	3
Units: participants				
Day 4: Uninfected; no viral RNA detected	0	0	0	0
Day 4: Asymptomatic; viral RNA detected	0	0	2	0
Day 4: Symptomatic; independent	1	0	1	0
Day 4: Symptomatic; assistance needed	0	0	0	0
Day 4: Hospitalised; no oxygen therapy	0	1	4	2
Day 4: Hospitalised; oxygen by mask or NP	1	0	0	1
Day 4: Hospitalised; oxygen by NIV or high flow	0	0	2	0
Day 4: Intubation and MV	0	0	0	0
Day 4: MV or vasopressors	0	0	0	0
Day 4: MV and vasopressors, dialysis, or ECMO	0	0	0	0
Day 4: Dead	0	0	0	0
Day 8: Uninfected; no viral RNA detected	0	1	0	0
Day 8: Asymptomatic; viral RNA detected	0	0	3	0
Day 8: Symptomatic; independent	1	0	4	1
Day 8: Symptomatic; assistance needed	0	0	0	0
Day 8: Hospitalised; no oxygen therapy	0	0	0	2
Day 8: Hospitalised; oxygen by mask or NP	1	0	1	0
Day 8: Hospitalised; oxygen by NIV or high flow	0	0	1	0
Day 8: Intubation and MV	0	0	0	0
Day 8: MV or vasopressors	0	0	1	0
Day 8: MV and vasopressors, dialysis, or ECMO	0	0	0	0
Day 8: Dead	0	0	0	0
Day 15: Uninfected; no viral RNA detected	0	1	2	0
Day 15: Asymptomatic; viral RNA detected	0	0	2	0
Day 15: Symptomatic; independent	1	0	1	1
Day 15: Symptomatic; assistance needed	0	0	1	0
Day 15: Hospitalised; no oxygen therapy	1	0	1	1
Day 15: Hospitalised; oxygen by mask or NP	0	0	0	1
Day 15: Hospitalised; oxygen by NIV or high flow	0	0	0	0
Day 15: Intubation and MV	0	0	0	0
Day 15: MV or vasopressors	0	0	2	0
Day 15: MV and vasopressors, dialysis, or ECMO	0	0	1	0
Day 15: Dead	0	0	0	0
Day 30: Uninfected; no viral RNA detected	0	1	3	1

Day 30: Asymptomatic; viral RNA detected	0	0	2	0
Day 30: Symptomatic; independent	2	0	1	0
Day 30: Symptomatic; assistance needed	0	0	0	0
Day 30: Hospitalised; no oxygen therapy	0	0	0	0
Day 30: Hospitalised; oxygen by mask or NP	0	0	0	2
Day 30: Hospitalised; oxygen by NIV or high flow	0	0	0	0
Day 30: Intubation and MV	0	0	0	0
Day 30: MV or vasopressors	0	0	1	0
Day 30: MV and vasopressors, dialysis, or ECMO	0	0	0	0
Day 30: Dead	0	0	0	0
Day 60: Uninfected; no viral RNA detected	1	1	3	1
Day 60: Asymptomatic; viral RNA detected	1	0	2	1
Day 60: Symptomatic; independent	0	0	1	0
Day 60: Symptomatic; assistance needed	0	0	0	0
Day 60: Hospitalised; no oxygen therapy	0	0	0	0
Day 60: Hospitalised; oxygen by mask or NP	0	0	0	1
Day 60: Hospitalised; oxygen by NIV or high flow	0	0	0	0
Day 60: Intubation and MV	0	0	0	0
Day 60: MV or vasopressors	0	0	0	0
Day 60: MV and vasopressors, dialysis, or ECMO	0	0	0	0
Day 60: Dead	0	0	0	0

Notes:

[9] - Day 4 N = 9; Day 30 N = 7; Day 60 N = 6.

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1[10]	7[11]	
Units: participants				
Day 4: Uninfected; no viral RNA detected	0	9999	0	
Day 4: Asymptomatic; viral RNA detected	0	9999	0	
Day 4: Symptomatic; independent	0	9999	0	
Day 4: Symptomatic; assistance needed	0	9999	0	
Day 4: Hospitalised; no oxygen therapy	0	9999	5	
Day 4: Hospitalised; oxygen by mask or NP	0	9999	1	
Day 4: Hospitalised; oxygen by NIV or high flow	1	9999	1	
Day 4: Intubation and MV	0	9999	0	
Day 4: MV or vasopressors	0	9999	0	
Day 4: MV and vasopressors, dialysis, or ECMO	0	9999	0	

Day 4: Dead	0	9999	0	
Day 8: Uninfected; no viral RNA detected	0	1	0	
Day 8: Asymptomatic; viral RNA detected	0	0	2	
Day 8: Symptomatic; independent	0	0	1	
Day 8: Symptomatic; assistance needed	0	0	0	
Day 8: Hospitalised; no oxygen therapy	0	0	1	
Day 8: Hospitalised; oxygen by mask or NP	0	0	1	
Day 8: Hospitalised; oxygen by NIV or high flow	1	0	2	
Day 8: Intubation and MV	0	0	0	
Day 8: MV or vasopressors	0	0	0	
Day 8: MV and vasopressors, dialysis, or ECMO	0	0	0	
Day 8: Dead	0	0	0	
Day 15: Uninfected; no viral RNA detected	0	1	1	
Day 15: Asymptomatic; viral RNA detected	0	0	2	
Day 15: Symptomatic; independent	0	0	1	
Day 15: Symptomatic; assistance needed	0	0	0	
Day 15: Hospitalised; no oxygen therapy	0	0	1	
Day 15: Hospitalised; oxygen by mask or NP	1	0	1	
Day 15: Hospitalised; oxygen by NIV or high flow	0	0	0	
Day 15: Intubation and MV	0	0	0	
Day 15: MV or vasopressors	0	0	0	
Day 15: MV and vasopressors, dialysis, or ECMO	0	0	0	
Day 15: Dead	0	0	0	
Day 30: Uninfected; no viral RNA detected	0	9999	2	
Day 30: Asymptomatic; viral RNA detected	0	9999	2	
Day 30: Symptomatic; independent	0	9999	0	
Day 30: Symptomatic; assistance needed	1	9999	1	
Day 30: Hospitalised; no oxygen therapy	0	9999	0	
Day 30: Hospitalised; oxygen by mask or NP	0	9999	0	
Day 30: Hospitalised; oxygen by NIV or high flow	0	9999	0	
Day 30: Intubation and MV	0	9999	0	
Day 30: MV or vasopressors	0	9999	0	
Day 30: MV and vasopressors, dialysis, or ECMO	0	9999	0	
Day 30: Dead	0	9999	0	
Day 60: Uninfected; no viral RNA detected	0	9999	4	
Day 60: Asymptomatic; viral RNA detected	0	9999	0	
Day 60: Symptomatic; independent	0	9999	1	

Day 60: Symptomatic; assistance needed	1	9999	0	
Day 60: Hospitalised; no oxygen therapy	0	9999	0	
Day 60: Hospitalised; oxygen by mask or NP	0	9999	0	
Day 60: Hospitalised; oxygen by NIV or high flow	0	9999	0	
Day 60: Intubation and MV	0	9999	0	
Day 60: MV or vasopressors	0	9999	0	
Day 60: MV and vasopressors, dialysis, or ECMO	0	9999	0	
Day 60: Dead	0	9999	0	

Notes:

[10] - Days 4, 30, and 60 N = 0.

[11] - Day 15 N = 6; Days 30 and 60 N = 5.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Requiring Oxygen Therapy

End point title	Number of Participants Requiring Oxygen Therapy

End point description:

The maximum number of participants requiring oxygen therapy on any day during each visit window is reported.

FAS Population: All randomised participants who received at least 1 dose of study treatment (plitidepsin or control) and completed follow-up for survival until Day 30 (±2). Participants who died before the end of the follow-up period were also included in the FAS population.

End point type	Secondary

End point timeframe:

Days 4 (±1), 8 (±1), 15 (±1), 30 (±2), and 60 (±3)

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	10	3
Units: participants				
Day 4	0	0	2	1
Day 8	1	0	3	1
Day 15	0	0	3	1
Day 30	0	0	1	1
Day 60	0	0	1	1

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	7	

Units: participants				
Day 4	1	0	3	
Day 8	1	0	3	
Day 15	1	1	1	
Day 30	1	0	1	
Day 60	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Sustained Discontinuation of Oxygen Supplementation

End point title	Time to Sustained Discontinuation of Oxygen Supplementation

End point description:

Time to sustained discontinuation is calculated as time from randomisation to the corresponding event using KM estimates. Corresponding events were defined as discontinuation of oxygen supplementation for at least 7 days. Participants with no available data for any time to event efficacy endpoint were censored at time 0, end of study (Day 60 ±3), or date of early study termination. Also, participants who had not achieved the time to event endpoint were censored at the last valid assessment.

FAS Population: All randomised participants who received at least 1 dose of study treatment (plitidepsin or control) and completed follow-up for survival until Day 30 (±2). Participants who died before the end of the follow-up period were also included in the FAS population. Values of "-99999" and "99999" indicate median and/or CI were not reached due to low number of events.

End point type	Secondary

End point timeframe:

Day 1 to Day 60 (±3)

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	10	3
Units: days				
median (confidence interval 95%)	13.0 (-99999 to 99999)	99999 (-99999 to 99999)	63.0 (1.0 to 99999)	99999 (34.0 to 99999)

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	7	
Units: days				
median (confidence interval 95%)	99999 (-99999 to 99999)	14.0 (-99999 to 99999)	14.0 (2.0 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experience a Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experience a Treatment-emergent Adverse Event (TEAE)

End point description:

Frequency of the following events (all-cause and treatment-related) are included:
• TEAEs
• TEAEs ≥ grade 3 according to the NCI CTCAE v5.0
• TEAEs of special interest
• Serious TEAEs
• Serious adverse reactions (SARs)
• AEs leading to treatment discontinuation (TD)
• Deaths (related to COVID-19/all)
Clinically relevant/significant changes from Baseline in laboratory parameters and vital signs were reported as AEs.

As Treated Population: All participants who received any exposure to study treatment (plitidepsin or control). As Treated population was analysed according to the treatment they actually received.

End point type	Secondary

End point timeframe:

Day 1 to Day 60 (±3)

End point values	Group 1: Plitidepsin 2.5 mg	Group 1: Control	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	1	10[12]	3[13]
Units: participants				
Any TEAE	1	1	10	4
Any treatment-related TEAE	1	0	4	1
Any TEAE ≥ grade 3	1	0	5	4
Any treatment-related TEAE ≥ grade 3	0	0	0	0
Any TEAE of special interest	1	0	4	2
Any treatment-related TEAE of special interest	1	0	1	1
Any serious TEAE	1	0	5	4
Any treatment-related serious TEAE	0	0	0	0
Any TEAE leading to TD	0	0	0	0
Any treatment-related TEAE leading to TD	0	0	0	0
Any TEAE leading to death	0	0	3	0
Any treatment-related TEAE leading to death	0	0	0	0

Notes:

[12] - N = 11 per As Treated Population.

[13] - N = 4 per As Treated Population.

End point values	Group 3: Plitidepsin 2.5 mg	Group 3: Control	Group 4: Plitidepsin 2.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	1	7[14]	
Units: participants				
Any TEAE	1	1	7	
Any treatment-related TEAE	0	0	2	
Any TEAE ≥ grade 3	1	1	4	
Any treatment-related TEAE ≥ grade 3	0	0	1	
Any TEAE of special interest	0	0	4	
Any treatment-related TEAE of special interest	0	0	0	
Any serious TEAE	1	1	2	
Any treatment-related serious TEAE	0	0	0	
Any TEAE leading to TD	0	0	0	
Any treatment-related TEAE leading to TD	0	0	0	
Any TEAE leading to death	1	1	1	
Any treatment-related TEAE leading to death	0	0	0	

Notes:

[14] - N = 8 per As Treated Population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 60 (±3)

Adverse event reporting additional description:

As Treated Population: All participants who received any exposure to study treatment (plitidepsin or control). As Treated population was analysed according to the treatment they actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Group 3: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Reporting group title	Group 4: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 4.

Group 4 – Other situations with immune deficiencies.

Reporting group title	Group 1: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Reporting group title	Group 3: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 3.

Group 3 – Participants who received other immune-suppressive therapies.

Reporting group title	Group 2: Plitidepsin 2.5 mg

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) and plitidepsin (administered as a 60-minute IV infusion, every 24 hours for 3 consecutive days, at a dose of 2.5 mg) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Reporting group title	Group 2: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 2.

Group 2 – Participants who received B-cell depleting therapies.

Reporting group title	Group 1: Control

Reporting group description:

Best standard care (as per applicable local, institutional, national, supranational COVID-19 treatment guidelines) ± other regulatory-approved antiviral (if clinically indicated) were administered to participants in Group 1.

Group 1 – Participants who received immune-suppression due to haematopoietic or organ transplantation.

Serious adverse events	Group 3: Control	Group 4: Plitidepsin 2.5 mg	Group 1: Plitidepsin 2.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	2 / 8 (25.00%)	1 / 2 (50.00%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Generalised oedema			

subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pneumoperitoneum			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumothorax			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 1 (100.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stenotrophomonas infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 3: Plitidepsin 2.5 mg	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	5 / 11 (45.45%)	4 / 4 (100.00%)
number of deaths (all causes)	1	3	0
number of deaths resulting from adverse events	1	3	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	1 / 1 (100.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 1 (100.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pneumoperitoneum			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 1 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			

subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Stenotrophomonas infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 1: Control		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Plasma cell myeloma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			

subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Coma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Pneumoperitoneum			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematochezia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
COVID-19				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Candida pneumonia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Device related infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stenotrophomonas infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group 3: Control	Group 4: Plitidepsin 2.5 mg	Group 1: Plitidepsin 2.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	6 / 8 (75.00%)	1 / 2 (50.00%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vein disorder			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Malaise			
subjects affected / exposed	0 / 1 (0.00%)	2 / 8 (25.00%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	3 / 8 (37.50%)	0 / 2 (0.00%)
occurrences (all)	0	3	0
Chills			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			

Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Rales			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Pharyngeal erythema			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Lung consolidation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 1 (0.00%)	2 / 8 (25.00%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	4 / 8 (50.00%)	0 / 2 (0.00%)
occurrences (all)	0	4	0
Dyspnoea exertional			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 1 (100.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Oxygen saturation decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Urine output decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
White blood cell count increased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Procedural nausea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cardiac failure			

subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Atrial fibrillation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Dizziness postural			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Slow speech			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	1 / 2 (50.00%)
occurrences (all)	0	2	1
Neutropenia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Eye disorders			

Conjunctival haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Renal impairment			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	1 / 2 (50.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Bone pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Campylobacter infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Bacteraemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 1 (100.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 1 (100.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Hypokalaemia			
subjects affected / exposed	1 / 1 (100.00%)	1 / 8 (12.50%)	0 / 2 (0.00%)
occurrences (all)	1	1	0
Hypophosphataemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 8 (0.00%)	0 / 2 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Group 3: Plitidepsin 2.5 mg	Group 2: Plitidepsin 2.5 mg	Group 2: Control
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	10 / 11 (90.91%)	4 / 4 (100.00%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Haematoma			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vein disorder			

subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)	5 / 11 (45.45%)	2 / 4 (50.00%)
occurrences (all)	0	7	4
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	2 / 11 (18.18%)	1 / 4 (25.00%)
occurrences (all)	0	2	1
Chills			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rales			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pharyngeal erythema			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Lung consolidation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Dyspnoea			
subjects affected / exposed	1 / 1 (100.00%)	3 / 11 (27.27%)	3 / 4 (75.00%)
occurrences (all)	2	3	7
Dyspnoea exertional			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypoxia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood urea increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oxygen saturation decreased			

subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urine output decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
White blood cell count increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Procedural nausea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Cardiac failure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Atrial fibrillation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dizziness postural			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			

subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Slow speech			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 1 (0.00%)	3 / 11 (27.27%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			

subjects affected / exposed	0 / 1 (0.00%)	2 / 11 (18.18%)	0 / 4 (0.00%)
occurrences (all)	0	5	0
Constipation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Renal impairment			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc degeneration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Myalgia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Bone pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Campylobacter infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Bacteraemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cystitis			
subjects affected / exposed	1 / 1 (100.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	1 / 1 (100.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Hypoglycaemia			

subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 11 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 11 (9.09%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Group 1: Control		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vein disorder			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Fatigue			

subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Rales			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pharyngeal erythema			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Lung consolidation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Epistaxis			

subjects affected / exposed occurrences (all) Hypoxia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0		
Investigations Blood creatinine increased subjects affected / exposed occurrences (all) Blood urea increased subjects affected / exposed occurrences (all) Cardiac murmur subjects affected / exposed occurrences (all) Lymphocyte count decreased subjects affected / exposed occurrences (all) Oxygen saturation decreased subjects affected / exposed occurrences (all) Urine output decreased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) White blood cell count increased subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Procedural nausea			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cardiac failure			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Atrial fibrillation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Dizziness postural			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Slow speech			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Migraine			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Gastrointestinal sounds abnormal subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 1 / 1 (100.00%) 1		
Skin and subcutaneous tissue disorders			

Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Intervertebral disc degeneration subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		
Infections and infestations Clostridium difficile infection subjects affected / exposed occurrences (all) Campylobacter infection subjects affected / exposed occurrences (all)	 0 / 1 (0.00%) 0 0 / 1 (0.00%) 0		

Bacteraemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cystitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Decreased appetite			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2022	The main objective and rationale for the substantial amendment was to correct the errors detected after the signature of the study protocol and to implement some changes (amendments) in response to clarifications requested by different drug agencies from the countries where the NEREIDA study was to be carried out and that had led to country-specific protocol versions.
22 March 2023	The main objective and rationale for the substantial amendment was to include all changes applied in the local and global amendments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was early terminated due to significant difficulties in the recruitment of participants.

Notes: