Clinical trial results:
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

Summary

EudraCT number	2020-005951-19
Trial protocol	FR BG GR PT ES RO
Global end of trial date	01 March 2023

Results information

Result version number	v1 (current)
This version publication date	15 February 2024
First version publication date	15 February 2024

Trial information

Trial identification

Sponsor protocol code	APL-D-003-20

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04784559
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar S.A.
Sponsor organisation address	Avda. De los Reyes, 1, Madrid, Spain, 28770
Public contact	Clinical Development Virology Business Unit, Pharma Mar S.A., + 34 918466000, virologytrials@pharmamar.com
Scientific contact	José Jimeno, MD, PhD, Pharma Mar S.A., + 34 918466000, jjimeno@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	07 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2023
Global end of trial reached?	Yes
Global end of trial date	01 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare efficacy of plitidepsin 1.5 mg or 2.5 mg versus the control assessing the need of supplementary oxygen.

Protection of trial subjects:

Patients were allowed to withdraw from the study at any time at his/her own request or at the discretion of the investigator for safety, behavioural, or administrative reasons. If the patient withdrew consent for disclosure of future information, the sponsor was to retain and continue to use any data collected before such a withdrawal of consent. Additionally, patients were allowed to request destruction of any samples taken and not tested and the investigator documented this in the site study records.

Additional reasons for discontinuation could have included, but were not limited to:
- Administration of treatments not allowed in the protocol
- Adverse event
- Lack of efficacy
- Investigator’s decision
- Patient refusal as reason for discontinuation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2021
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	Romania: 61
Country: Number of subjects enrolled	Spain: 114
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Brazil: 1
Worldwide total number of subjects	205
EEA total number of subjects	193

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)	126
From 65 to 84 years	79
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The target population of this study was adult patients requiring hospitalisation and oxygen supplementation for management of moderate COVID-19.

Period 1

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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Plitidepsin 2.5 mg

Arm description:

Patients received plitidepsin 2.5 mg/day IV in addition to dexamethasone on Days 1 to 3

Arm type	Experimental
Investigational medicinal product name	Plitidepsin 2.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received plitidepsin 2.5 mg/day IV in addition to dexamethasone on Days 1 to 3.

Best supportive care, consistent with National Institute of Health COVID-19 Treatment Guidelines (www.covid19treatmentguidelines.nig.gov) or local country guidelines was provided (when needed).

Arm title	Plitidepsin 1.5 mg

Arm description:

Patients received plitidepsin 1.5 mg/day intravenously (IV) in addition to dexamethasone on Days 1 to 3

Arm type	Experimental
Investigational medicinal product name	Plitidepsin 1.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received plitidepsin 1.5 mg/day IV in addition to dexamethasone on Days 1 to 3.

Best supportive care, consistent with National Institute of Health COVID-19 Treatment Guidelines (www.covid19treatmentguidelines.nig.gov) or local country guidelines was provided (when needed).

Arm title	Control arm

Arm description:

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.

Arm type	Active comparator
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

All patients were planned to receive dexamethasone phosphate 8 mg/day IV (equivalent to 6.6 mg dexamethasone base) on Days 1 to 3 (administered as a premedication in the plitidepsin arms), followed by dexamethasone phosphate 7.2 mg/day (equivalent to 6 mg/day dexamethasone base) orally (PO)/IV from Day 4 and up to a total cumulative dose of 60 mg dexamethasone base (as per physician judgement according to patient clinical condition and evolution).

Additionally, in accordance with local treatment guidelines, patients randomised to the control arm could have received a regulatory-approved antiviral treatment, such as remdesivir (200 mg IV on Day 1 followed by 100 mg/day IV on Days 2 to 5) or favipiravir (1600 mg twice daily [BID] PO on Day 1, followed by 600 mg BID PO for 2 to 5 days).

Best supportive care, consistent with National Institute of Health COVID-19 Treatment Guidelines (www.covid19treatmentguidelines.nig.gov) or local country guidelines was provided (when needed).

Number of subjects in period 1	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm
Started	68	70	67
Completed	60	64	61
Not completed	8	6	6
Patient worsened, PI decision	1	-	-
Did not meet all inclusion criteria	-	1	-
The patient was transferred to IRCU	-	1	-
Discontinued as was found to be ineligible	-	-	1
Patient admitted in other hospital	1	-	-
Death	2	1	2
Patient deterioration	1	-	-
Serious adverse event	-	1	-
Lost to follow-up	-	-	2
Patient refusal (withdrawal of consent)	3	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Plitidepsin 2.5 mg
Reporting group description:	
Patients received plitidepsin 2.5 mg/day IV in addition to dexamethasone on Days 1 to 3	

Reporting group title	Plitidepsin 1.5 mg
Reporting group description:	
Patients received plitidepsin 1.5 mg/day intravenously (IV) in addition to dexamethasone on Days 1 to 3	

Reporting group title	Control arm
Reporting group description:	
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.	

Reporting group values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm
Number of subjects	68	70	67
Age categorical Units: Subjects			
≥18 to 59 years	32	34	32
≥60 to 64 years	13	9	6
≥65 to 69 years	8	11	11
≥70 to 74 years	9	8	4
≥75 to 79 years	3	6	7
≥80 years	3	2	7
Age continuous Units: years			
arithmetic mean	58.9	58.1	59.3
standard deviation	± 13.33	± 14.80	± 15.02
Gender categorical Units: Subjects			
Female	25	26	25
Male	43	44	42
Race Units: Subjects			
Asian	1	3	0
White	63	62	64
Multiple	4	5	3
Ethnicity Units: Subjects			
Hispanic or Latino	33	35	21
Not Hispanic of Latino	35	35	46
Child-bearing potential			
For female participants only			
Units: Subjects			
Yes	4	5	4
No, surgially sterile/post-menopausal	21	18	19
No, other	0	3	2

NA (male participant)	43	44	42
Body mass index group at screening (kg/m2) Units: Subjects			
≥18.5 and <25	10	10	10
≥25 and <30	31	35	26
≥30 and <35	15	13	17
≥35 and <40	9	4	8
≥40	1	5	4
Missing	2	3	2
Periods of inclusion Units: Subjects			
Beginning of accrual – August 2021	2	1	2
September 2021 - March 2022	56	55	51
April 2022 - End of accrual	10	14	14
Vaccination status Units: Subjects			
Fully vaccinated	35	36	32
Non-fully vaccinated	6	3	4
Not vaccinated	27	31	31
Height at screening Units: Centimeter			
arithmetic mean	167.79	169.56	169.25
standard deviation	± 8.067	± 8.534	± 10.095
Weight at screening Units: Kilograms			
arithmetic mean	82.72	86.05	87.38
standard deviation	± 14.380	± 19.778	± 19.672
Body mass index at screening Units: kg/m2			
arithmetic mean	29.45	29.68	30.26
standard deviation	± 4.555	± 5.617	± 6.116
Body surface area at screening (m2) Units: Participants			
arithmetic mean	1.922	1.961	1.968
standard deviation	± 0.1787	± 0.2252	± 0.2299
Systolic blood pressure (mmHg) at screening Units: mmHg			
arithmetic mean	123.4	126.9	127.9
standard deviation	± 18.44	± 16.25	± 16.24
Diastolic blood pressure (mmHg) at screening Units: mmHg			
arithmetic mean	74.2	76.1	75.0
standard deviation	± 9.53	± 9.36	± 11.26
Pulse rate (beats/min) at screening Units: beats/min			
arithmetic mean	81.6	83.9	84.2
standard deviation	± 13.72	± 11.36	± 13.50
Temperature (C) at screening Units: celsius			

arithmetic mean	36.91	36.90	36.92
standard deviation	± 0.878	± 0.899	± 0.875
Respiration rate (breaths/min) at screening			
Units: breaths/min			
arithmetic mean	19.5	19.0	19.9
standard deviation	± 3.49	± 3.40	± 3.32
Oxygen saturation (%) at screening			
Units: Percentage measure			
median	96.29	96.26	96.44
standard deviation	± 1.779	± 1.721	± 1.749
Fraction of inspired oxygen (%) at screening			
Units: Percentage			
arithmetic mean	26.92	26.91	27.94
standard deviation	± 3.861	± 3.370	± 9.526
SARS-CoV-2 viral load at Day 1 (log 10 copies/mL)			
Units: Summary was based on full analysis set			
arithmetic mean	5.02	4.97	5.06
standard deviation	± 1.880	± 1.985	± 2.253

Reporting group values	Total		
Number of subjects	205		
Age categorical			
Units: Subjects			
≥18 to 59 years	98		
≥60 to 64 years	28		
≥65 to 69 years	30		
≥70 to 74 years	21		
≥75 to 79 years	16		
≥80 years	12		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	76		
Male	129		
Race			
Units: Subjects			
Asian	4		
White	189		
Multiple	12		
Ethnicity			
Units: Subjects			
Hispanic or Latino	89		
Not Hispanic of Latino	116		
Child-bearing potential			
For female participants only			
Units: Subjects			

Yes	13		
No, surgially sterile/post-menopausal	58		
No, other	5		
NA (male participant)	129		
Body mass index group at screening (kg/m2)			
Units: Subjects			
≥18.5 and <25	30		
≥25 and <30	92		
≥30 and <35	45		
≥35 and <40	21		
≥40	10		
Missing	7		
Periods of inclusion			
Units: Subjects			
Beginning of accrual – August 2021	5		
September 2021 - March 2022	162		
April 2022 - End of accrual	38		
Vaccination status			
Units: Subjects			
Fully vaccinated	103		
Non-fully vaccinated	13		
Not vaccinated	89		
Height at screening			
Units: Centimeter			
arithmetic mean			
standard deviation	-		
Weight at screening			
Units: Kilograms			
arithmetic mean			
standard deviation	-		
Body mass index at screening			
Units: kg/m2			
arithmetic mean			
standard deviation	-		
Body surface area at screening (m2)			
Units: Participants			
arithmetic mean			
standard deviation	-		
Systolic blood pressure (mmHg) at screening			
Units: mmHg			
arithmetic mean			
standard deviation	-		
Diastolic blood pressure (mmHg) at screening			
Units: mmHg			
arithmetic mean			
standard deviation	-		
Pulse rate (beats/min) at screening			
Units: beats/min			
arithmetic mean			

standard deviation	-		
Temperature (C) at screening Units: celsius arithmetic mean standard deviation	- 		
Respiration rate (breaths/min) at screening Units: breaths/min arithmetic mean standard deviation	- 		
Oxygen saturation (%) at screening Units: Percentage measure median standard deviation	- 		
Fraction of inspired oxygen (%) at screening Units: Percentage arithmetic mean standard deviation	- 		
SARS-CoV-2 viral load at Day 1 (log 10 copies/mL) Units: Summary was based on full analysis set arithmetic mean standard deviation	- 		

End points

End points reporting groups

Reporting group title	Plitidepsin 2.5 mg

Reporting group description:

Patients received plitidepsin 2.5 mg/day IV in addition to dexamethasone on Days 1 to 3

Reporting group title	Plitidepsin 1.5 mg

Reporting group description:

Patients received plitidepsin 1.5 mg/day intravenously (IV) in addition to dexamethasone on Days 1 to 3

Reporting group title	Control arm

Reporting group description:

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.

Primary: Time to sustained withdrawal of supplementary oxygen (11-category WHO Clinical Progression Scale ≤4) with no subsequent reutilisation during remaining study period.

End point title	Time to sustained withdrawal of supplementary oxygen (11-category WHO Clinical Progression Scale ≤4) with no subsequent reutilisation during remaining study period.

End point description:

Time to sustained withdrawal of supplementary oxygen (as defined by the WHO clinical progression scale (Score ≤4).

The WHO clinical progression scale provides a measure of illness severity across a range from 0 (uninfected) to 10 (dead).

End point type	Primary

End point timeframe:

From administration date to Day 31(±3)

End point values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	70	67	
Units: days				
median (confidence interval 95%)	5 (4 to 7)	5 (4 to 6)	7 (6 to 8)	

Statistical analyses

Statistical analysis title	Plitidepsin 2.5 mg arm versus control arm

Statistical analysis description:

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

Comparison groups	Plitidepsin 2.5 mg v Control arm
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8751 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.727
upper limit	1.53

Notes:

[1] - 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 .

[2] - 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment arm and levels of the randomisation stratification factors. Unadjusted pvalue, for multiplicity adjustment uses the Hochberg step-up procedure

Statistical analysis title	Plitidepsin 1.5 mg arm versus control arm

Statistical analysis description:

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

Comparison groups	Control arm v Plitidepsin 1.5 mg
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0625 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.96

Notes:

[3] - 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 .

[4] - 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment arm and levels of the randomisation stratification factors. Unadjusted pvalue, for multiplicity adjustment uses the Hochberg step-up procedure

Secondary: Time to sustained (i.e., with no subsequent readmission to Day 31) hospital discharge (since randomisation)

End point title	Time to sustained (i.e., with no subsequent readmission to Day 31) hospital discharge (since randomisation)

End point description:

Time to sustained (i.e., with no subsequent readmission to Day 31) hospital discharge (since randomisation)

000 = not estimated
999 = not estimated

End point type	Secondary

End point timeframe:

From administration date to Day 31(±3)

End point values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	70	67	
Units: days				
median (confidence interval 95%)	7 (7 to 9)	7 (000 to 999)	7 (7 to 9)	

Statistical analyses

Statistical analysis title	Plitidepsin 2.5 mg versus control arm
Comparison groups	Plitidepsin 2.5 mg v Control arm
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5945 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.948
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.655
upper limit	1.37

Notes:

[5] - 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment arm and levels of the randomisation stratification factors. Unadjusted pvalue, for multiplicity adjustment uses the Hochberg step-up procedure

Statistical analysis title	Plitidepsin 1.5 mg versus control arm
Comparison groups	Control arm v Plitidepsin 1.5 mg
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3358 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.827
upper limit	1.7

Notes:

[6] - 2-sided p-values calculated using a stratified log-rank test, including the fixed effect of the treatment arm and levels of the randomisation stratification factors. Unadjusted pvalue, for multiplicity adjustment uses the Hochberg step-up procedure

Secondary: Clinical Status by the 11-category WHO Clinical Progression Scale

End point title	Clinical Status by the 11-category WHO Clinical Progression Scale

End point description:

The WHO clinical progression scale provides a measure of illness severity across a range from 0 (uninfected) to 10 (dead).

*pO2/FiO2 >150 or SpO2/FiO2 >200
**pO2/FiO2 <150 (SpO2/FiO2 <200) or vasopressors
***pO2/FiO2 <150 and vasopressors, dialysis, or ECMO

End point type	Secondary

End point timeframe:

Day 8 (±1)

End point values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	67	65	
Units: participants				
0 = uninfected, no viral RNA detected	6	10	3	
1 = asymptomatic, viral RNA detected	12	15	12	
2 = symptomatic, independent	20	17	19	
3 = symptomatic, assistance needed	0	1	1	
4 = hospitalised, no oxygen therapy	4	8	7	
5 = hospitalised, oxygen by mask or nasal prongs	10	8	20	
6 = hospitalised, oxygen by NIV or high flow	5	7	1	
7 = intubation and mechanical ventilation*	4	1	2	
8 = mechanical ventilation**	1	0	0	
9 = mechanical ventilation***	0	0	0	
10 = dead	1	0	0	

Statistical analyses

Statistical analysis title	Plitidepsin 2.5 mg versus control

Statistical analysis description:

Adjusted Odds Ratio and 95% CI 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.

Comparison groups	Plitidepsin 2.5 mg v Control arm
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.7252 [8]
Method	proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.604
upper limit	2.06

Notes:

[7] - 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

[8] - 2-sided p-value. Adjusted odds ratio, 95% CI and 2-sided p-values based on a proportional odds model with fixed effects of treatment arm and randomisation stratification factors

Statistical analysis title	Plitidepsin 1.5 mg versus control
Comparison groups	Control arm v Plitidepsin 1.5 mg
Number of subjects included in analysis	132
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.091 [9]
Method	proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	3.11

Notes:

[9] - Adjusted odds ratio, 95% CI and 2-sided p-values based on a proportional odds model with fixed effects of treatment arm and randomisation stratification factors

Secondary: Total Duration of Advanced Oxygen Support (High-flow Nasal Oxygen, Extracorporeal Membrane Oxygenation - ECMO-, Non-invasive Ventilation or Mechanical Ventilation)

End point title	Total Duration of Advanced Oxygen Support (High-flow Nasal Oxygen, Extracorporeal Membrane Oxygenation - ECMO-, Non-invasive Ventilation or Mechanical Ventilation)

End point description:

Total Duration of Advanced Oxygen Support (High-flow Nasal Oxygen, Extracorporeal Membrane Oxygenation - ECMO-, Non-invasive Ventilation or Mechanical Ventilation)

End point type	Secondary

End point timeframe:

From administration date to Day 31(±3)

End point values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	11	11	
Units: days				
arithmetic mean (standard deviation)	12.2 (± 9.71)	10 (± 8.21)	8.3 (± 12.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients in Each Study Group Requiring Admission to ICU

End point title	Percentage of Patients in Each Study Group Requiring Admission to ICU

End point description:

Percentage of Patients in Each Study Group Requiring Admission to ICU

End point type	Secondary

End point timeframe:

Day 4, Day 8(±1) , Day 15(±1) and Day 31(±3)

End point values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	67	65	
Units: participants				
number (confidence interval 95%)				
From Day 1 to Day 4	1 (0.0402 to 8.53)	1 (0.0378 to 8.04)	3 (0.962 to 12.9)	
From Day 1 to Day 8	7 (4.59 to 21.6)	3 (0.933 to 12.5)	4 (1.70 to 15.0)	
From Day 1 to Day 15	7 (4.59 to 21.6)	4 (1.65 to 14.6)	4 (1.70 to 15.0)	
From Day 1 to Day 31	7 (4.59 to 21.6)	5 (2.47 to 16.6)	4 (1.70 to 15.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Adverse Events

End point title	Frequency of Adverse Events

End point description:

Adverse Event Types according to the National Cancer Institute [NCI]-Common Terminology Criteria for AEs (CTCAE v.5.0).

The number of participants who experienced treatment-emergent adverse events (TEAEs) are presented.

End point type	Secondary

End point timeframe:

From administration date to Day 31(±3)

End point values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	67	65	
Units: participants	45	44	40	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of TEAEs of ≥Grade 3 According to NCI-CTCAE for Adverse Events (Version 5.0), TEAEs of Special Interest, Serious TEAEs, Serious Treatment-related TEAEs, TEAEs Leading to Treatment Discontinuation, and Deaths

End point title	Frequency of TEAEs of ≥Grade 3 According to NCI-CTCAE for Adverse Events (Version 5.0), TEAEs of Special Interest, Serious TEAEs, Serious Treatment-related TEAEs, TEAEs Leading to Treatment Discontinuation, and Deaths

End point description:

Frequency of treatment-emergent adverse events (TEAEs) of ≥grade 3 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0), TEAEs of special interest, serious TEAEs, serious treatment-related TEAEs, TEAEs leading to treatment discontinuation, and deaths.

*Any serious treatment-related TEAE to any study treatment
**Any TEAE leading to discontinuation of any study treatment

End point type	Secondary

End point timeframe:

From administration date to Day 31(±3)

End point values	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	67	65	
Units: participants				
Any TEAE Grade ≥3	22	17	11	
Any TEAE of special interest	22	25	18	
Any serious TEAE	11	6	5	
Serious treatment-related TEAE to treatment**	1	1	0	
TEAE leading to discontinuation**	1	1	1	
Any TEAE leading to death	2	1	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Screening to Day 31 +/- 3 days

Adverse event reporting additional description:

Adverse events for the as-treated population are presented. One randomised participant experienced an AE of adult respiratory distress syndrome but never received any study treatment, so is not included here.

All AEs and adverse reactions, based on clinical signs and symptoms and laboratory measurements, were measured daily from Day 1 to Day 31.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Plitidepsin 2.5 mg

Reporting group description:

Patients received plitidepsin 2.5 mg/day IV in addition to dexamethasone on Days 1 to 3.

Adverse events for the as-treated population are presented.

Reporting group title	Plitidepsin 1.5 mg

Reporting group description:

Patients received plitidepsin 1.5 mg/day intravenously (IV) in addition to dexamethasone on Days 1 to 3

Adverse events for the as-treated population are presented.

Reporting group title	Control arm

Reporting group description:

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.

Adverse events for the as-treated population are presented.

Serious adverse events	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 63 (17.46%)	6 / 67 (8.96%)	5 / 65 (7.69%)
number of deaths (all causes)	2	1	2
number of deaths resulting from adverse events	2	1	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (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
General disorders and administration site conditions			

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal ischaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	6 / 63 (9.52%)	4 / 67 (5.97%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (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
Infections and infestations			
COVID-19 pneumonia			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (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
COVID-19			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (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
Pneumonia pseudomonal			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (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
Pneumonia streptococcal			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			

subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Plitidepsin 2.5 mg	Plitidepsin 1.5 mg	Control arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 63 (68.25%)	43 / 67 (64.18%)	38 / 65 (58.46%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acrochordon			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Thymoma			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Vascular disorders			
Phlebitis			
subjects affected / exposed	11 / 63 (17.46%)	9 / 67 (13.43%)	2 / 65 (3.08%)
occurrences (all)	11	9	2
Hypotension			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	3 / 65 (4.62%)
occurrences (all)	1	2	3
Hypertension			
subjects affected / exposed	0 / 63 (0.00%)	3 / 67 (4.48%)	2 / 65 (3.08%)
occurrences (all)	0	4	4
Deep vein thrombosis			
subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	2	0	0
Peripheral venous disease			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	3 / 63 (4.76%)	4 / 67 (5.97%)	4 / 65 (6.15%)
occurrences (all)	4	7	5
Asthenia			
subjects affected / exposed	3 / 63 (4.76%)	3 / 67 (4.48%)	2 / 65 (3.08%)
occurrences (all)	3	3	2
Chest discomfort			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	4 / 65 (6.15%)
occurrences (all)	1	1	4
Malaise			
subjects affected / exposed	0 / 63 (0.00%)	3 / 67 (4.48%)	3 / 65 (4.62%)
occurrences (all)	0	3	3
Extravasation			
subjects affected / exposed	2 / 63 (3.17%)	2 / 67 (2.99%)	1 / 65 (1.54%)
occurrences (all)	2	2	1
Oedema peripheral			
subjects affected / exposed	1 / 63 (1.59%)	3 / 67 (4.48%)	1 / 65 (1.54%)
occurrences (all)	1	3	1
Catheter site haemorrhage			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Catheter site phlebitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Discomfort			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	2
Generalised oedema			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Illness			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Perineal erythema			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Prostatitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Pruritus genital			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	8 / 63 (12.70%)	7 / 67 (10.45%)	5 / 65 (7.69%)
occurrences (all)	10	7	6
Dyspnoea			
subjects affected / exposed	3 / 63 (4.76%)	1 / 67 (1.49%)	4 / 65 (6.15%)
occurrences (all)	3	1	5
Cough			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	4 / 65 (6.15%)
occurrences (all)	1	2	5
Pulmonary embolism			
subjects affected / exposed	3 / 63 (4.76%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	3	1	0
Bronchial hyperreactivity			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Hiccups			
subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Bronchial disorder			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Dyspnoea exertional			

subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Laryngeal oedema			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Lung disorder			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Pleuritic pain			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Pneumomediastinum			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Rales			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Respiratory distress			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	7 / 63 (11.11%)	6 / 67 (8.96%)	5 / 65 (7.69%)
occurrences (all)	8	6	6
Anxiety			
subjects affected / exposed	5 / 63 (7.94%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	6	0	1
Confusional state			
subjects affected / exposed	2 / 63 (3.17%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	2	1	0
Irritability			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	1	1	0

Delirium			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Investigations			
Serum ferritin abnormal			
subjects affected / exposed	15 / 63 (23.81%)	13 / 67 (19.40%)	4 / 65 (6.15%)
occurrences (all)	18	16	5
C-reactive protein increased			
subjects affected / exposed	11 / 63 (17.46%)	7 / 67 (10.45%)	5 / 65 (7.69%)
occurrences (all)	11	11	5
Blood lactate dehydrogenase increased			
subjects affected / exposed	6 / 63 (9.52%)	6 / 67 (8.96%)	6 / 65 (9.23%)
occurrences (all)	6	7	7
Alanine aminotransferase increased			
subjects affected / exposed	4 / 63 (6.35%)	7 / 67 (10.45%)	5 / 65 (7.69%)
occurrences (all)	4	8	6
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 63 (7.94%)	8 / 67 (11.94%)	3 / 65 (4.62%)
occurrences (all)	7	9	3
Procalcitonin increased			
subjects affected / exposed	7 / 63 (11.11%)	4 / 67 (5.97%)	2 / 65 (3.08%)
occurrences (all)	7	4	2
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 63 (7.94%)	3 / 67 (4.48%)	4 / 65 (6.15%)
occurrences (all)	5	3	4
Blood glucose increased			
subjects affected / exposed	4 / 63 (6.35%)	4 / 67 (5.97%)	4 / 65 (6.15%)
occurrences (all)	4	4	5
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 63 (0.00%)	2 / 67 (2.99%)	3 / 65 (4.62%)
occurrences (all)	0	2	3
Fibrin D dimer increased			
subjects affected / exposed	2 / 63 (3.17%)	2 / 67 (2.99%)	1 / 65 (1.54%)
occurrences (all)	2	3	1

Lymphocyte count decreased			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	2 / 65 (3.08%)
occurrences (all)	1	2	2
Lipase increased			
subjects affected / exposed	3 / 63 (4.76%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	4	1	0
Adjusted calcium decreased			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	0 / 65 (0.00%)
occurrences (all)	1	2	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
Oxygen saturation			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Amylase increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Blood albumin decreased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Blood potassium decreased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Blood sodium decreased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Chest X-ray abnormal			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Electrocardiogram PR prolongation			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1

Hepatic enzyme abnormal			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Hepatic enzyme increased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Interleukin level decreased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Interleukin level increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	2	0	0
International normalised ratio increased			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Troponin T increased			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Epicondylitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Eschar			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	2	0	0
Limb injury			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Nerve injury			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Traumatic haematoma			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Wound			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 63 (3.17%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	2	1	1
Atrioventricular block			
subjects affected / exposed	0 / 63 (0.00%)	2 / 67 (2.99%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Atrial fibrillation			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Cardiac failure			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			

subjects affected / exposed	6 / 63 (9.52%)	7 / 67 (10.45%)	5 / 65 (7.69%)
occurrences (all)	8	8	5
Dizziness			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	0 / 65 (0.00%)
occurrences (all)	1	2	0
Paraesthesia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Epilepsy			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Neuromyopathy			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Somnolence			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	2 / 63 (3.17%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	2	2	1
Leukocytosis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	2 / 65 (3.08%)
occurrences (all)	0	1	2
Anaemia			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	2	1	0
Leukopenia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	0	1	1

Neutropenia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Normocytic anaemia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Tinnitus			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 63 (17.46%)	10 / 67 (14.93%)	4 / 65 (6.15%)
occurrences (all)	12	10	4
Nausea			
subjects affected / exposed	9 / 63 (14.29%)	8 / 67 (11.94%)	1 / 65 (1.54%)
occurrences (all)	9	8	1
Diarrhoea			
subjects affected / exposed	9 / 63 (14.29%)	3 / 67 (4.48%)	3 / 65 (4.62%)
occurrences (all)	9	3	3
Abdominal pain			
subjects affected / exposed	2 / 63 (3.17%)	3 / 67 (4.48%)	2 / 65 (3.08%)
occurrences (all)	2	3	2
Vomiting			
subjects affected / exposed	3 / 63 (4.76%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	3	2	0
Dyspepsia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Flatulence			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Oropharyngeal pain			

subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	0	1	1
Frequent bowel movements			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Mouth haemorrhage			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	2	0	0
Stomatitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Hypertransaminasaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	1 / 65 (1.54%)
occurrences (all)	3	2	1
Erythema			
subjects affected / exposed	0 / 63 (0.00%)	2 / 67 (2.99%)	0 / 65 (0.00%)
occurrences (all)	0	3	0
Dry skin			

subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Subcutaneous emphysema			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	4 / 63 (6.35%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	4	1	1
Dysuria			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
Pollakiuria			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Urge incontinence			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	4 / 63 (6.35%)	2 / 67 (2.99%)	1 / 65 (1.54%)
occurrences (all)	5	2	1
Back pain			
subjects affected / exposed	2 / 63 (3.17%)	2 / 67 (2.99%)	1 / 65 (1.54%)
occurrences (all)	2	2	1
Pain in extremity			
subjects affected / exposed	2 / 63 (3.17%)	2 / 67 (2.99%)	0 / 65 (0.00%)
occurrences (all)	2	2	0
Myopathy			

subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	2	0	1
Limb discomfort			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Muscle contracture			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Neck pain			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	3 / 63 (4.76%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Tooth infection			
subjects affected / exposed	0 / 63 (0.00%)	2 / 67 (2.99%)	0 / 65 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	1	0	1
Bacteraemia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Bacteriuria			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Herpes simplex			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0

Herpes zoster			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Pneumonia bacterial			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Tracheobronchitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	14 / 63 (22.22%)	12 / 67 (17.91%)	6 / 65 (9.23%)
occurrences (all)	14	12	6
Decreased appetite			
subjects affected / exposed	1 / 63 (1.59%)	2 / 67 (2.99%)	0 / 65 (0.00%)
occurrences (all)	1	2	0
Hyperkalaemia			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	1 / 65 (1.54%)
occurrences (all)	1	1	1
Diabetes mellitus			
subjects affected / exposed	1 / 63 (1.59%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	1	1	0
Hypokalaemia			
subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Hyponatraemia			

subjects affected / exposed	2 / 63 (3.17%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	3	0	0
Acquired mixed hyperlipidaemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 63 (0.00%)	1 / 67 (1.49%)	0 / 65 (0.00%)
occurrences (all)	0	1	0
Hypernatraemia			
subjects affected / exposed	0 / 63 (0.00%)	0 / 67 (0.00%)	1 / 65 (1.54%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Hypoproteinaemia			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0
Metabolic alkalosis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 67 (0.00%)	0 / 65 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2021	• Revised study title to specify the adult patients requiring hospitalisation for management of moderate COVID-19. • Indication was revised from "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (Coronavirus disease-2019 [COVID-19])" to "Treatment of patients hospitalised for management of moderate COVID-19 infection". • Updated study objectives, respective endpoints, and overall study design and plan description. • Revised end of study definition, diagnosis, and main criteria for inclusion and exclusion. • Updated replacement procedures and follow-up schedule of patients prematurely discontinued from the study treatment regimen or withdrawn from study. • Updated treatments administered, method of treatment assignment, background information, study rationale to align with study design and updated investigator brochure. • Updated section about blinding based on WHO guidance and experience in the APLICOV-PC trial. • List of allowed medications, prohibited medications, and supportive care were updated. • Updated study assessments and procedure section. • Updated section on determination of sample size. • Updated Schedule of Assessments. • Added new appendix (#7) of Barthel index for functional assessment.
12 February 2021	• Updated inclusion criterion #3: excluded any patient with hyperbilirubinemia, including patients with Gilbert's syndrome as requested by agency (Medicines and Healthcare products Regulatory Agency). • Updated exclusion criterion #10 to add appropriate risk mitigation for bradycardia. • Updated contraception guidance in line with the Australian Summary of Product Characteristics.

18 March 2021	• Updated introduction section to add text for APLICOV findings, safety, and efficacy in patients with COVID-19 and benefit-risk considerations • Updated objective and endpoints, as below: o Modified "COVID-19 infection" to "COVID-19 related signs or symptoms" o Include "Proportion of patients with a serologic response anti-SARS-CoV-2" as other secondary objective o Include "Proportion of patients with a serologic response anti-SARS-CoV-2" as other secondary endpoint o Changed patients to be included in QTc substudy (from at least 25 to 50 patients) • Updated section of investigation plan to allow equivalence between doses of dexamethasone phosphate and dexamethasone base, patients to be included in QTc substudy (from at least 25 to 50 patients), and IDMC responsibilities • Updated section for selection of study population • Stopping rules: Added futility analysis for efficacy and safety to be performed when 33% of patients have been randomised and reached a follow-up of 31 days • Deleted interim analysis for efficacy • Updated section of study treatment, concomitant therapies, and other restrictions • Updated section of study assessment and procedures: o Changed the timeframe defined in Schedule of Assessments (from 48 hours to 24 hours) o Clarified time to perform the PCR for COVID-19 (not only at screening but also within the previous 24 hours) o Modified "COVID-19 infection" to "COVID-19 related signs or symptoms" o Clinical laboratory evaluations: Included sodium, potassium, calcium (adjusted), magnesium and troponin, BNP/NT-pro BNP o Prestudy screening assessments o Evaluations during the study treatment updated for serum chemistry, vital signs, and SpO2 o Updated section of sample size and analyses for number of patients o Included Appendix 11 to explain the Charlson comorbidity index o Added futility analysis for efficacy & safety o Included users of antiviral therapies or immunomodulatory drugs in subgroup analyses for primary endpoint
13 April 2021	• Revised randomisation stratification factor as Geographical Region (Europe versus Rest of the World). • Updated IDMC charter. • A multiplicity adjustment was added in key secondary efficacy outcome measures and Hochberg procedure. • Futility analysis text was updated. • AEs of special interest were added under other secondary objectives/endpoints. • Corrected usage of "in person visit or remotely" and added troponin assessment, at applicable instances. • Revised the text that the troponin tests were to be performed at local laboratory. • Administration of remdesivir if the patient was randomised to the control arm (yes versus no), a subgroup was added for the primary efficacy endpoint analysis.

27 July 2021	• Two (non-key) secondary objectives were added. • Protocol was adapted to include patients that have received dexamethasone prior to randomisation. • Inclusion criteria updated to allow inclusion of patients with documented diagnosis of SARS-CoV-2 infection by either qualitative PCR or antigen test, to allow patients with maximum of 10 days from onset of COVID-19 symptoms to initiation of study treatment on Day 1, and criteria related to CPK levels, urine samples for pregnancy, and effective contraception methods. • Below exclusion criteria were updated to exclude patients having received treatment for COVID-19 in another trial 4 weeks prior to study enrolment, with severe disease, including mild to severe acute respiratory distress syndrome, history of live vaccination, and with uncontrolled known primary or secondary immunodeficiency. • Disease diagnostic criteria clarified for investigators in the case that the patient had experienced more than one COVID-19 episode. • Clarified for investigators that dose reduction was not allowed. • Concomitant medication text revised to indicate that all COVID-19 vaccinations were to be recorded. • Allowed medication section was amended to allow SARS-CoV-2 vaccination except vaccines with live attenuated virus. • Prohibited medications section updated for usage of approved therapies. • Prebaseline Barthel index score was to be recorded for the previous month before screening. Additionally, SARS-CoV-2 variant was to be recorded, if available.
13 October 2021	• Peru-specific country amendment was released.
29 March 2022	• Study rationale updated with new treatments for COVID-19 and updated results for APLICOV-PC study. • Primary and secondary efficacy objectives and respective endpoints were revised to reflect the significant changes in patient population hospitalised for moderate COVID-19. • Other secondary efficacy objective endpoints were updated for clarity. • Inclusion and exclusion criteria were revised to align with evolving clinical practice for COVID-19. • A new stratification factor of Barthel index was added for randomisation. • Futility analysis was revised to align with revised study design, study objectives, and endpoints. • Standard of care was revised based on the additional treatments and locally approved agents per local guidance. • In the study design, description of treatments in the study arms and follow-up period was clarified. Clarified that dexamethasone is administered as part of premedication on Days 1 to 3. • The AEs to be monitored during the follow-up period were clarified. End of study definition was revised. • Randomisation time was extended to 20 months to support recruitment. • Safety and efficacy assessments were updated to align with revised endpoints. End of study assessments were updated. Accordingly, the Schedule of Assessment table was updated. • Statistical analysis was revised to align with revised endpoints.

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.

Sponsor prematurely ended study on 31Jan23 due to decreased incidence of study population. Due to system restriction, EoT is entered as 01Mar23, primary completion date, despite Sponsor considering EoT the date of reporting early termination, 31Jan23

Notes: