Clinical trial results:
PHASE II CLINICAL TRIAL, SINGLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED TO EXPLORE THE EFFECTIVENESS AND SAFETY OF MELATONIN I.V. IN PATIENTS WITH COVID-19 ENTERED INTO THE ICU (MELCOVID STUDY)

Summary

EudraCT number	2020-001808-42
Trial protocol	ES
Global end of trial date	06 February 2021

Results information

Result version number	v1
This version publication date	07 November 2021
First version publication date	07 November 2021

Trial information

Trial identification

Sponsor protocol code	PHM-2020-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04568863
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PHARMAMEL S.L.
Sponsor organisation address	Gran Vía 48, 7th floor, Granada, Spain, 18071
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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	26 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2021
Global end of trial reached?	Yes
Global end of trial date	06 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate whether intravenous (IV) melatonin treatment reduces mortality in patients with COVID-19 admitted to the Intensive care unit (ICU).

Protection of trial subjects:

Patients were free to discontinue their participation in the study at any time. Withdrawal from the study did not affect or prejudice the patient’s further treatment. Patients could be withdrawn from study treatment and assessments at any time, if deemed necessary by the Investigator.

Patients suspended study therapy and/or withdrew from the same for the following reasons:
- Withdrawal of informed consent (decision of the patient to withdraw regardless of the reason).
- Unacceptable toxicity
- Disease progression which, in the investigator's opinion, did not allow the patient to continue in the study.
- The patient did not comply with the protocol, treatment or monitoring requirements.
- Any other reason to interrupt the treatment which, in the opinion of the investigator, was the best for the patient.
- Any clinical adverse event, test anomaly or breakthrough disease which, in the opinion of the investigator, indicated that continuing treatment with such therapy and with participation in the study was not in the best interest of the patient.
- Completion of the study by the research team.

Background therapy:

All included patients received standard-of-care (SOC) treatment defined by the protocol in force at the centre at the time of study initiation.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	15 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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)	12
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a national study with all patients being included at one Spanish site. Eighteen patients signed the ICF and were assessed for eligibility. There were no screening failures. The included patients (n=18) were randomized 2:1 in the study and received treatment as follows: melatonin (n=12) and placebo (n=6).

Pre-assignment

Screening details:

Adults infected by SARS-CoV-2 admitted to the ICU for less than 7 days and without signs of improvement in respiratory failure weere included. Patients were excluded if they were included in another COVID-19 study, had liver transaminases >5 times the ULN, stage IV kidney failure or were on dialysis, pregnancy, terminal illness, autoimmune disease

Period 1

Period 1 title	Study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Non-study staff prepared the unmasked randomization codes, designed so that patients were assigned proportionally 2:1 to the experimental group or the control group respectively. They also prepared sealed envelopes containing the unmasked randomization code.
The research team was provided with a list of masked randomization codes, so that the research staff assigned each eligible patient, in order of inclusion, a masked randomization code.

Arms

Are arms mutually exclusive?	Yes
Arm title	Melatonin

Arm description:

This arm included all patients who were randomized to melatonin. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred: discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Arm type	Experimental
Investigational medicinal product name	Melatonin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

The experimental treatment was melatonin 6 mg/mL solution for injection/infusion. The study medication was administered intravenously by the ICU health personnel in charge of the patient. Melatonin was administered according to the established guideline based on weight: 5 mg/kg current weight/day divided into 4 doses a day (1 dose/6hrs) and with a maximum daily dose of 500 mg.

After the first 3 days of treatment, three intensive care physicians in charge of the patient decided whether to extend the treatment until day 6 of the study (total of 7 days of treatment) based on the patient's clinical evaluation.

Arm title	Placebo

Arm description:

This arm included all patients who were randomized to placebo. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred:

discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients included in the placebo group received placebo according to their weight: 5 mg/kg current weight/day divided into 4 doses a day (1 dose/6hrs). The study medication was administered intravenously by the ICU health personnel in charge of the patient.

After the first 3 days of treatment, three intensive care physicians in charge of the patient decided whether to extend the treatment until day 6 of the study (total of 7 days of treatment) based on the patient's clinical evaluation.

Number of subjects in period 1	Melatonin	Placebo
Started	12	6
Completed	12	6

Baseline characteristics

Reporting groups

Reporting group title	Melatonin

Reporting group description:

This arm included all patients who were randomized to melatonin. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred: discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Reporting group title	Placebo

Reporting group description:

This arm included all patients who were randomized to placebo. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred: discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Reporting group values	Melatonin	Placebo	Total
Number of subjects	12	6	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	4	12
From 65-84 years	4	2	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.5	62.8	
standard deviation	± 9.73	± 11.11	-
Gender categorical Units: Subjects			
Female	5	2	7
Male	7	4	11
Ethnicity Units: Subjects			
Hispanic or Latino	6	2	8
Not Hispanic or Latino	6	4	10
Race Units: Subjects			
White	12	6	18
Weight Units: kilogram(s)			
arithmetic mean	80.8	84.7	
standard deviation	± 17.30	± 26.92	-

Height			
Units: centimeter			
arithmetic mean	169.3	169.8	
standard deviation	± 10.26	± 12.89	-
Body Mass Index (BMI)			
Units: kilogram(s)/square meter			
arithmetic mean	28.0	28.9	
standard deviation	± 4.37	± 6.71	-

End points

End points reporting groups

Reporting group title	Melatonin

Reporting group description:

This arm included all patients who were randomized to melatonin. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred: discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Reporting group title	Placebo

Reporting group description:

This arm included all patients who were randomized to placebo. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred: discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Primary: Mortality frequencies

End point title	Mortality frequencies

End point description:

The absolute and relative frequency of deaths in the study was tabulated by treatment group with the 95%CI of the percentages. There were a total of 6 deaths, 5 deaths in the melatonin group and 1 death in the placebo group. Three of them (2 in the melatonin group and 1 in the placebo group) occurred out of the study period.

End point type	Primary

End point timeframe:

From ICF signature until the end of the study.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Percentage of deaths				
number (confidence interval 95%)				
Number of deaths	41.7 (15.17 to 72.33)	16.7 (0.42 to 64.12)		

Statistical analyses

Statistical analysis title	Fisher's exact test

Statistical analysis description:

Fisher's exact test was used to investigate whether there was a difference between treatment groups in the proportion of deaths.

Comparison groups	Melatonin v Placebo

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6
Method	Fisher exact

Primary: Causes of death

End point title	Causes of death[1]

End point description:

End point type	Primary

End point timeframe:

From ICF signature until the end of the study.

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: Causes of death were reported by treatment group. No statistical analysis was performed.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	1		
Units: Subjects				
Haemorrhage intracranial	1	0		
Multiple organ dysfunction syndrome	2	0		
Unknown (deaths occurred out of the study period)	2	1		

Statistical analyses

No statistical analyses for this end point

Primary: Overall survival

End point title	Overall survival

End point description:

The Kaplan-Meyer method for overall survival (OS) was performed to test the differences of the experimental treatment over placebo. OS was calculated in days as the time from the day of administration of the first dose of IV melatonin or IV placebo until the date of death due to any cause. For patients alive at the time of the analysis or if lost to follow up, the date of death was censored on the last date the patients were known to be alive.

End point type	Primary

End point timeframe:

From ICF signature until the end of the study.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Percentage of subects				
number (confidence interval 95%)				
0 day	100.0 (100.0 to 100.0)	100.0 (100.0 to 100.0)		
10 days	91.7 (53.9 to 98.8)	100.0 (100.0 to 100.0)		
20 days	83.3 (48.2 to 95.6)	100.0 (100.0 to 100.0)		
30 days	74.1 (39.1 to 90.9)	100.0 (100.0 to 100.0)		
40 days	63.5 (28.9 to 84.7)	80.0 (20.4 to 96.9)		
50 days	63.5 (28.9 to 84.7)	80.0 (20.4 to 96.9)		
60 days	63.5 (28.9 to 84.7)	80.0 (20.4 to 96.9)		
70 days	63.5 (28.9 to 84.7)	80.0 (20.4 to 96.9)		
80 days	63.5 (28.9 to 84.7)	0 (0 to 0)		
90 days	63.5 (28.9 to 84.7)	0 (0 to 0)		
100 days	63.5 (28.9 to 84.7)	0 (0 to 0)		
110 days	63.5 (28.9 to 84.7)	0 (0 to 0)		
120 days	31.7 (1.7 to 72.5)	0 (0 to 0)		
130 days	31.7 (1.7 to 72.5)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Log-rank test
Statistical analysis description:	
Log rank test was performed to test the differences between the treatment groups.	
Comparison groups	Melatonin v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.427
Method	Logrank

Secondary: Length of ICU admission

End point title	Length of ICU admission
End point description:	
ICUBSS= ICU admission time before the study start in days; ICUT=Total ICU admission time in days.	
End point type	Secondary

End point timeframe:

ICUBSS, period from date of ICU admission until the date of first treatment study administration; ICUT, from the ICU admission date until the end of the study.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[2]	6[3]		
Units: day				
arithmetic mean (standard deviation)				
ICUBSS (Death=No)	6.0 (± 1.15)	5.2 (± 1.79)		
ICUBSS (Death=Yes)	3.2 (± 2.17)	6.0 (± 0)		
ICUT (Death=No)	37.3 (± 32.59)	34.8 (± 23.70)		
ICUT (Death=Yes)	43.4 (± 43.33)	43.0 (± 0)		

Notes:

[2] - Death=No (7 subjects); Death=Yes (5 subjects)

[3] - Death=No (5 subjects); Death=Yes (1 subject)

Statistical analyses

No statistical analyses for this end point

Secondary: Length of Hospital admission

End point title	Length of Hospital admission

End point description:

THA= Total time of hospital admission in days.

End point type	Secondary

End point timeframe:

From the calendar day of hospitalization until the date of hospital discharge.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[4]	6[5]		
Units: day				
arithmetic mean (standard deviation)				
THA (Death=No)	60.1 (± 45.11)	59.6 (± 25.34)		
THA (Death=Yes)	48.2 (± 44.43)	48.0 (± 0)		

Notes:

[4] - Death=No (7 subjects); Death=Yes (5 subjects)

[5] - Death=No (5 subjects); Death=Yes (1 subject)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of mechanical ventilation (MV)

End point title	Duration of mechanical ventilation (MV)

End point description:

TMVBSS = Time with mechanical ventilation before the start of the study in days; TFMV = Time free of mechanical ventilation in days. The total time with MV was tabulated by the type of MV.

End point type	Secondary

End point timeframe:

TMVBSS, from the date with MV before the 1st administration of study drug until the date of 1st administration of study drug.
TFMV, cumulative time during study. Total time with MV, start/end dates reported in the 'Mechanical ventilation' CRF module.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[6]	6[7]		
Units: day				
arithmetic mean (standard deviation)				
TMVBSS (Death=No)	5.7 (± 1.60)	4.8 (± 2.49)		
TMVBSS (Death=Yes)	3.3 (± 1.89)	6.0 (± 0)		
TFMV (Death=No)	40.9 (± 17.93)	24.4 (± 11.08)		
TFMV (Death=Yes)	0.0 (± 0.00)	0.0 (± 0.00)		
Duration of invasive MVs (Death=No)	21.3 (± 19.00)	27.6 (± 20.76)		
Duration of invasive MVs (Death=Yes)	41.2 (± 44.80)	18.0 (± 18.38)		
Duration of non-invasive MVs (Death=No)	16.5 (± 20.51)	9.0 (± 0)		
Duration of non-invasive MVs (Death=Yes)	0 (± 0)	2.0 (± 0)		

Notes:

[6] - Death=No (7 subjects); Death=Yes (5 subjects).
Missings: n=1 (TMVBSS, Death=Yes).
[7] - Death=No (5 subjects); Death=Yes (1 subject)

Attachments (see zip file)	Mean Days of MV Items (Alive Patients; n=12) /Figure MV.pptx

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the score on the SOFA scale

End point title	Change in the score on the SOFA scale

End point description:

The SOFA scale score numerically quantified the number and severity of failed organs. Final visit performed before day 28 that was recorded in 'Final Visit - Day 28' has been included in the subsequent visit to the last visit performed.

End point type	Secondary

End point timeframe:

Score on the SOFA scale at days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[8]	6[9]		
Units: SOFA score (absolute value)				
arithmetic mean (standard deviation)				
Screening - Day 0	3.8 (± 1.47)	4.8 (± 1.33)		
Visit 1 - Day 1	4.3 (± 2.02)	5.2 (± 1.72)		
Visit 2 - Day 3	4.8 (± 2.09)	5.0 (± 1.67)		
Visit 3 - Day 7	6.3 (± 4.36)	4.3 (± 3.01)		
Visit 4 - Day 14	4.6 (± 2.91)	6.8 (± 2.22)		
Visit 5 - Day 21	5.6 (± 4.27)	6.3 (± 2.06)		
Visit Day 28	4.5 (± 1.29)	4.5 (± 2.38)		

Notes:

[8] - Day 0 (n=12), Day 1 (n=12), Day 3 (n=12), Day 7 (n=12), Day 14 (n=10), Day 21 (n=8) and Day 28 (n=4)
[9] - Day 0 (n=6), Day 1 (n=6), Day 3 (n=6), Day 7 (n=6), Day 14 (n=4), Day 21 (n=4) and Day 28 (n=4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the score on the MURRAY scale

End point title	Change in the score on the MURRAY scale

End point description:

Final visit performed before day 28 that was recorded in 'Final Visit - Day 28' has been included in the subsequent visit to the last visit performed.

End point type	Secondary

End point timeframe:

Score on the MURRAY scale at days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[10]	6[11]		
Units: MURRAY score (absolute value)				
arithmetic mean (standard deviation)				
Screening - Day 0	2.47 (± 0.281)	2.72 (± 0.248)		
Visit 1 - Day 1	2.65 (± 0.582)	2.44 (± 0.364)		
Visit 2 - Day 3	2.47 (± 0.491)	2.15 (± 0.508)		
Visit 3 - Day 7	2.37 (± 0.692)	1.98 (± 1.288)		
Visit 4 - Day 14	2.35 (± 1.019)	2.83 (± 0.236)		
Visit 5 - Day 21	2.49 (± 1.037)	2.46 (± 0.417)		
Visit Day 28	2.68 (± 0.250)	2.16 (± 0.560)		

Notes:

[10] - Day 0 (n=12), Day 1 (n=12), Day 3 (n=12), Day 7 (n=12), Day 14 (n=9), Day 21 (n=8) and Day 28 (n=4)
[11] - Day 0 (n=6), Day 1 (n=6), Day 3 (n=6), Day 7 (n=6), Day 14 (n=4), Day 21 (n=4) and Day 28 (n=4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the score on the Glasgow coma scale (GCS)

End point title	Change in the score on the Glasgow coma scale (GCS)

End point description:

Final visit performed before day 28 that was recorded in 'Final Visit - Day 28' has been included in the subsequent visit to the last visit performed.

End point type	Secondary

End point timeframe:

Score on the GCS at days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[12]	6[13]		
Units: GCS score (absolute value)				
arithmetic mean (standard deviation)				
Screening - Day 0	15.0 (± 0.00)	0 (± 0)		
Visit 1 - Day 1	15.0 (± 0.00)	10.0 (± 0)		
Visit 2 - Day 3	10.0 (± 0)	11.0 (± 4.24)		
Visit 3 - Day 7	0 (± 0)	11.0 (± 0)		
Visit 4 - Day 14	0 (± 0)	0 (± 0)		
Visit 5 - Day 21	15.0 (± 0)	0 (± 0)		
Visit Day 28	0 (± 0)	14.0 (± 0)		

Notes:

[12] - Day 0 (n=2), Day 1 (n=2), Day 3 (n=1), Day 7 (n=0), Day 14 (n=0), Day 21 (n=1) and Day 28 (n=0)
[13] - Day 0 (n=0), Day 1 (n=1), Day 3 (n=2), Day 7 (n=1), Day 14 (n=0), Day 21 (n=0) and Day 28 (n=1)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the score on the APACHE II scale

End point title	Change in the score on the APACHE II scale

End point description:

Too few patients had available assessments, being most of them from the screening visit. Final visit performed before day 28 that was recorded in 'Final Visit - Day 28' has been included in the subsequent visit to the last visit performed.

End point type	Secondary

End point timeframe:

Score on the APACHE II scale at days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[14]	6[15]		
Units: APACHE II score (absolute value)				
arithmetic mean (standard deviation)				
Screening - Day 0	13.8 (± 4.78)	14.7 (± 5.43)		
Visit 1 - Day 1	0 (± 0)	0 (± 0)		
Visit 2 - Day 3	0 (± 0)	13.0 (± 0)		
Visit 3 - Day 7	0 (± 0)	0 (± 0)		
Visit 4 - Day 14	0 (± 0)	0 (± 0)		
Visit 5 - Day 21	0 (± 0)	0 (± 0)		
Visit Day 28	0 (± 0)	0 (± 0)		

Notes:

[14] - Day 0 (n=10), Day 1 (n=0), Day 3 (n=0), Day 7 (n=0), Day 14 (n=0), Day 21 (n=0) and Day 28 (n=0)

[15] - Day 0 (n=6), Day 1 (n=0), Day 3 (n=1), Day 7 (n=0), Day 14 (n=0), Day 21 (n=0) and Day 28 (n=0)

Statistical analyses

No statistical analyses for this end point

Secondary: Thromboembolic processes

End point title	Thromboembolic processes

End point description:

Number of events, location and severity (affected organ and vascular territory) of thromboembolic events caused by COVID-19. It was not possible to assess whether IV melatonin treatment was associated with a reduction in the frequency and severity of thromboembolic processes caused by COVID-19, as only one single thromboembolic event was observed during the study (Respiratory, thoracic and mediastinal disorders > Pulmonary embolism > Moderate).

End point type	Secondary

End point timeframe:

From ICF signature until the end of the study.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Number of thromboembolic events				
Pulmonary embolism	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic inflammatory response

End point title	Systemic inflammatory response

End point description:

The systemic inflammatory response was assessed through the change observed from baseline, presented as the percentage value from baseline (calculated as [Visit X value / Screening value]*100), in ferritin, D-dimer, C-reactive protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6) on days 1, 3, 7, 14, 21 and 28. Please see documents attached.

End point type	Secondary

End point timeframe:

Systemic inflammatory parameters on days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Subjects				
Subjects included in the analysis	12	6		

Attachments (see zip file)	Ferritin.doc D-Dimer.doc C-Reactive Protein.doc Procalcitonin.doc Interleukin-6.doc

Statistical analyses

No statistical analyses for this end point

Secondary: Change in haematological parameters

End point title	Change in haematological parameters

End point description:

The change in the haematological parameters was evaluated through the variation from baseline in the levels of erythrocytes, Hb, platelets, fibrinogen, cephalin time, prothrombin time, antithrombin III, ADAMTS13 and Factor Xa (see Table 1 attached). Moreover, levels of basophils, eosinophils, haematocrit, lymphocytes, mean corpuscular haemoglobin concentration (MCHC), mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), monocytes, neutrophils and leucocytes were also evaluated throughout the study (see Table 2 attached).

End point type	Secondary

End point timeframe:

Haematological parameters on days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Subjects				
Subjects included in the analysis	12	6		

Attachments (see zip file)	Lymphocytes.doc Neutrophils.doc Table 1/Table 1. Blood count, free Hb, platelets, fibrinogen, Table 2/Table 2. Basophils, eosinophils, haematocrit,

Statistical analyses

No statistical analyses for this end point

Secondary: Change in biochemical parameters

End point title	Change in biochemical parameters

End point description:

The change in the biochemical parameters was evaluated through the variation from baseline in the levels of creatine kinase (CK), lactate dehydrogenase (LDH), glutamate-oxalacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), bilirubin, vitamin D and 1,25-OH-Vit D (calcitriol), calcium, albumin, blood urea nitrogen (BUN), creatinine and troponin on days 1, 3, 7, 14, 21 and 28. Please see documents attached.

End point type	Secondary

End point timeframe:

Biochemical parameters on days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Subjects				
Subjects included in the analysis	12	6		

Attachments (see zip file)	Bilirubin/Bilirubin.doc Biochemical parameters/Biochemical parameters.rtf

Statistical analyses

No statistical analyses for this end point

Secondary: Change in arterial blood gas parameters and electrolytes

End point title	Change in arterial blood gas parameters and electrolytes

End point description:

The change in the arterial blood gas parameters and electrolytes was evaluated through the variation from baseline in pH, SaO2, PaCO2, PO2, HCO3, glucose, Na, K, chlorine, lactate, anion gap and PaO2/FiO2 on days 1, 3, 7, 14, 21 and 28. Please see document attached.

End point type	Secondary

End point timeframe:

Arterial blood gas parameters and electrolytes on days 0, 1, 3, 7, 14, 21 and 28.

End point values	Melatonin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	6		
Units: Subjects				
Subjects included in the analysis	12	6		

Attachments (see zip file)	Arterial blood gas parameters and electrolytes/Arterial blood

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The collection of information on AEs should start on the basis of obtaining informed consent. All serious AEs must be reported to the sponsor within 24 hours of investigator’s awareness, regardless of their relationship to the experimental drug.

Adverse event reporting additional description:

All identified AEs should be noted and described in the patient's medical history. The following information must be collected for all AEs: date of onset , intensity, causal relationship with the study drug in the opinion of the investigator, treatment required for the AE, serious criteria of the AE and information on its resolution or outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Melatonin

Reporting group description:

This arm included all patients who were randomized to melatonin. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred: discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Reporting group title	Placebo

Reporting group description:

This arm included all patients who were randomized to placebo. The patients included in the study were administered the assigned treatment for up to 7 days, unless any of the following events occurred: discharge of the ICU patient, death of the patient, unacceptable toxicity or ustified treatment interruption according to the researcher's criteria.

Serious adverse events	Melatonin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	0 / 6 (0.00%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events	3	0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			

subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Melatonin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	5 / 6 (83.33%)	
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	3 / 12 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Hypertension			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Shock haemorrhagic			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Oedema			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			

subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Procedural failure			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Penile oedema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Scrotal oedema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Bronchial haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Bronchospasm			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pneumothorax			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
C-reactive protein increased			

subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme abnormal			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 12 (8.33%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Bradycardia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 12 (41.67%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Hypersplenism			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Leucocytosis			
subjects affected / exposed	3 / 12 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Lymphopenia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Neutrophilia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Thrombocytosis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Duodenal ulcer			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Faecal vomiting			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Intestinal obstruction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Haematuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oliguria			

subjects affected / exposed	2 / 12 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	2	3	
Polyuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
Candida infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Enterobacter bacteraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Enterobacter infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Enterobacter tracheobronchitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Haemophilus infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Klebsiella infection			
subjects affected / exposed	3 / 12 (25.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	

Peritonitis bacterial			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pneumonia haemophilus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Pneumonia klebsiella			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Pneumonia pseudomonal			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Pseudomonas infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Septic shock			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Staphylococcal bacteraemia			
subjects affected / exposed	3 / 12 (25.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Tracheobronchitis bacterial			
subjects affected / exposed	2 / 12 (16.67%)	2 / 6 (33.33%)	
occurrences (all)	2	3	
Urinary tract infection bacterial			
subjects affected / exposed	4 / 12 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection fungal			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection pseudomonal			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hypernatraemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Hyperuricaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	4 / 12 (33.33%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Hypophosphataemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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 interpretation of current results is limited by the short-term 7-days treatment period and the size of the population (n=18). The treatment of melatonin up to 7 days is not enough to reveal its anti-inflammatory and antioxidant effects in full.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32758298

http://www.ncbi.nlm.nih.gov/pubmed/32770854