Clinical trial results:
Sarilumab Treatment In cytoKinE storm caused by infection with COVID-19.

Summary

EudraCT number	2020-001255-40
Trial protocol	ES
Global end of trial date	10 November 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	STRIKE-SARS-COV2

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Clínica Universidad de Navarra
Sponsor organisation address	Avenida de Pío XII, 36, Pamplona, Spain, 31008
Public contact	UCEC, Clínica Universidad de Navarra, 34 948255 4002723, ucicec@unav.es
Scientific contact	UCEC, Clínica Universidad de Navarra, 34 948255 4002723, ucicec@unav.es

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	16 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2020
Global end of trial reached?	Yes
Global end of trial date	10 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Principal objective: evaluate the impact of sarilumab on the progression of COVID 19-associated respiratory failure as measured by the change in a severity rating on a 7-point severity index.
Secondary objective:
- Assess the impact of sarilumab on markers of systemic inflammation and the coagulation cascade in the context of COVID-19.
- Assess the impact of sarilumab on mortality caused by COVID-19.
- Assess the impact of sarilumab on oxygenation.
- Evaluate the safety of sarilumab in patients with severe pneumonia caused by COVID-19.

Protection of trial subjects:

Given the limited clinical evidence regarding the intravenous administration of sarilumab, the first five patients in the trial received an initial dose of 200 mg of sarilumab at V1 (day 1) and an optional second dose of 200 mg of sarilumab at V2 (24 hours later). To decide whether to administer 400 mg of sarilumab at V1 and an optional second dose of 400 mg at V2 in subsequent patients, a safety evaluation by an internal review committee was performed to assess the safety profile through clinical and laboratory abnormalities. The dose could be reduced to 200 mg in V2 according to medical discretion and the patient's clinical condition.

Background therapy:

Participants received full supportive care during the study, as well as treatment with antibiotics and analgesics, as appropriate.
The use of corticosteroids as rescue was allowed if it was considered that there was no response to the study treatment.

Evidence for comparator: -

Actual start date of recruitment	28 April 2020
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	Spain: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	41
From 65 to 84 years	23
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The inclusion of the first patient was on 28/04/2020 and the last patient was recruited on 19/10/2020. The participating sites were Clínica Universitaria de Navarra and Hospital Universitario Infanta Leonor.

Pre-assignment

Screening details:

65 patients were enrolled in the study, but 5 of them were screening failures and did not receive the study treatment.

Pre-assignment period milestones

Number of subjects started	65
Number of subjects completed	60

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Physician decision: 2

Period 1

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

Arms

Arm title	Sarilumab

Arm description:

Treatment of severe COVID-19 with sarilumab

Arm type	Experimental
Investigational medicinal product name	Sarilumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Infusion

Dosage and administration details:

Each patient received two separate doses of sarilumab 24 hours apart. Each dose was administered through intravenous infusion for one hour and consisted of 200 mg of sarilumab diluted in 100 mL of a solution at 0.9% of NaCl.

Number of subjects in period 1[1]	Sarilumab
Started	60
Completed	56
Not completed	4
Consent withdrawn by subject	4

Notes:

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

Justification: 65 patients were enrolled in the study, but 5 of them were screening failures and did not receive the study treatment.

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
Adults (18-64 years)	38	38	
From 65-84 years	21	21	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	59.5		
standard deviation	± 13.5	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	46	46	
Race Units: Subjects			
Caucasian	40	40	
Latin	8	8	
Hispanic	5	5	
Others	4	4	
Missing	3	3	
Patients reporting each severity rating on a 7-point severity ordinal scale			
7-point severity ordinal scale: 1. Death 2. Hospitalised, on invasive mechanical ventilation or ECMO 3. Hospitalised, on non-invasive ventilation or high flow oxygen devices 4. Hospitalised, requiring supplemental oxygen 5. Hospitalised, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise) 6. Hospitalised, not requiring supplemental oxygen – no longer requires ongoing medical care 7. Not hospitalised			
Units: Subjects			
Severity 1	0	0	
Severity 2	1	1	
Severity 3	6	6	
Severity 4	40	40	
Severity 5	13	13	
Severity 6	0	0	
Severity 7	0	0	
Smoking status			
The 36.7% has never smoked, where the rest smoked a mean (SD) 9.5 (9.9) cigarette per day since a mean (SD) of 23.1 (15.0) years with a mean (SD) of pack-years 16.2 (13.8).			
Units: Subjects			

Current some day smoker	1	1	
Former smoker	17	17	
Smoker	2	2	
Never smoker	22	22	
Unknown if ever smoked	18	18	
Medical history: hypertension Units: Subjects			
No	39	39	
Yes	21	21	
Medical history: Diabetes mellitus Units: Subjects			
No	50	50	
Yes	10	10	
Medical history: cardiac disease Units: Subjects			
No	59	59	
Yes	1	1	
Medical history: Chronic Obstructive Pulmonary Disease Units: Subjects			
No	56	56	
Yes	4	4	
Medical history: cancer Units: Subjects			
No	57	57	
Yes	3	3	
COVID-19 history: fever Units: Subjects			
No	8	8	
Yes	52	52	
COVID-19 history: cough Units: Subjects			
No	15	15	
Yes	45	45	
COVID-19 history: dysgeusia Units: Subjects			
No	53	53	
Yes	7	7	
COVID-19 history: anosmia Units: Subjects			
No	51	51	
Yes	9	9	
COVID-19 history: odynophagia Units: Subjects			
No	58	58	
Yes	2	2	
COVID-19 history: nausea Units: Subjects			
No	56	56	
Yes	4	4	
COVID-19 history: diarrhea			

Units: Subjects			
No	53	53	
Yes	7	7	
COVID-19 history: myalgia Units: Subjects			
No	42	42	
Yes	18	18	
COVID-19 history: asthenia Units: Subjects			
No	37	37	
Yes	23	23	
COVID-19 history: other related symptoms Units: Subjects			
No	19	19	
Yes	41	41	
PCR SARS CoV 2 Units: Subjects			
Positive	60	60	
Negative	0	0	
Chest radiography done Units: Subjects			
No	17	17	
Yes	43	43	
Chest radiography done: COVID-19 pneumonia Units: Subjects			
No	1	1	
Yes	42	42	
Missing	17	17	
CT Scan done Units: Subjects			
No	27	27	
Yes	33	33	
CT Scan done: COVID-19 pneumonia Units: Subjects			
No	1	1	
Yes	32	32	
Missing	27	27	
CT scan score for pulmonary involvement: rigth upper lobe Units: Subjects			
1-5% involvement	4	4	
6-25% involvement	14	14	
26-50% involvement	7	7	
51-75% involvement	5	5	
Missing	30	30	
CT scan score for pulmonary involvement: middle lobe Units: Subjects			
1-5% involvement	10	10	
6-25% involvement	8	8	

26-50% involvement	7	7	
51-75% involvement	3	3	
Missing	32	32	
CT scan score for pulmonary involvement: right lower lobe Units: Subjects			
1-5% involvement	4	4	
6-25% involvement	9	9	
26-50% involvement	8	8	
51-75% involvement	4	4	
100% involvement	6	6	
Missing	29	29	
CT scan score for pulmonary involvement: left upper lobe Units: Subjects			
1-5% involvement	7	7	
6-25% involvement	9	9	
26-50% involvement	6	6	
51-75% involvement	7	7	
100% involvement	1	1	
Missing	30	30	
CT scan score for pulmonary involvement: left lower lobe Units: Subjects			
1-5% involvement	4	4	
6-25% involvement	11	11	
26-50% involvement	4	4	
51-75% involvement	5	5	
100% involvement	5	5	
Missing	31	31	
Weight Units: kilogram(s)			
arithmetic mean	83.9		
standard deviation	± 14.7	-	
Height Units: centimetres			
arithmetic mean	169.8		
standard deviation	± 9.5	-	
Oxygen parameters: SaO2 (from pulsioximeter) Units: Percentage %			
arithmetic mean	94.1		
standard deviation	± 1.9	-	
Oxygen parameters: pH Units: --			
arithmetic mean	7.4		
standard deviation	± 0.1	-	
Oxygen parameters: PaO2 Units: mmHg			
arithmetic mean	71.4		
standard deviation	± 34.4	-	
Oxygen parameters: PaCO2 Units: mmHg			

arithmetic mean	37.2		
standard deviation	± 7.4	-	
Oxygen parameters: SaO2 (from arterial blood gases)			
Units: Percentage %			
arithmetic mean	88.6		
standard deviation	± 15.1	-	
Oxygen parameters: lactic acid (from arterial blood gases)			
Units: mmol/L			
arithmetic mean	1.5		
standard deviation	± 0.6	-	
Oxygen parameters: PaO2/FiO2 Index			
Units: --			
arithmetic mean	257.5		
standard deviation	± 151.1	-	
Oxygen parameters: SaO2/FiO2 Index			
Units: --			
arithmetic mean	152.7		
standard deviation	± 49.8	-	

End points

End points reporting groups

Reporting group title	Sarilumab
Reporting group description:	
Treatment of severe COVID-19 with sarilumab	
Subject analysis set title	Day 1
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Population: the patients who attended visit 1.	
Subject analysis set title	Day 2
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Population: the patients who attended visit 2.	
Subject analysis set title	Day 3
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Population: the patients who attended visit 3.	
Subject analysis set title	Day 4
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Population: the patients who attended visit 4.	
Subject analysis set title	Day 7
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Population: the patients who attended visit 5.	
Subject analysis set title	Day 28
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Population: the patients who attended visit 6.	
Subject analysis set title	Day 1 (N = N Day 2)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients who attended visit 1 and whose data were compared with the data of patients who attended visit 2.	
Subject analysis set title	Day 1 (N = N Day 3)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients who attended visit 1 and whose data were compared with the data of patients who attended visit 3.	
Subject analysis set title	Day 1 (N = N day 4)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients who attended visit 1 and whose data were compared with the data of patients who attended visit 4.	
Subject analysis set title	Day 1 (N = N Day 7)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients who attended visit 1 and whose data were compared with the data of patients who attended visit 5.	
Subject analysis set title	Day 1 (N = N Day 28)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients who attended visit 1 and whose data were compared with the data of patients who attended visit 6.

Primary: Change in a severity rating on a 7-point ordinal scale: day 7

End point title	Change in a severity rating on a 7-point ordinal scale: day 7

End point description:

Change in a severity rating on a 7-point ordinal scale:
1. Death
2. Hospitalised, on invasive mechanical ventilation or ECMO
3. Hospitalised, on non-invasive ventilation or high flow oxygen devices
4. Hospitalised, requiring supplemental oxygen
5. Hospitalised, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalised, not requiring supplemental oxygen – no longer requires ongoing medical care
7. Not hospitalised

End point type	Primary

End point timeframe:

Day 7

End point values	Day 1	Day 7		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	55		
Units: Subjects				
Severity 1	0	0		
Severity 2	1	1		
Severity 3	6	2		
Severity 4	37	13		
Severity 5	11	17		
Severity 6	0	20		
Severity 7	0	2		

Statistical analyses

Statistical analysis title	Patients who worsened

Statistical analysis description:

It was performed an analysis of contingency tables to see the evolution in 7-point ordinal severity score between day 1 and day 7, using McNemar test.

Comparison groups	Day 1 v Day 7
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	5.3

Statistical analysis title	Patients who remained stable

Statistical analysis description:

It was performed an analysis of contingency tables to see the evolution in 7-point ordinal severity score between day 1 and day 7, using McNemar test.

Comparison groups	Day 1 v Day 7
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage
Point estimate	30.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.7
upper limit	43.1

Statistical analysis title	Patients who improved

Statistical analysis description:

It was performed an analysis of contingency tables to see the evolution in 7-point ordinal severity score between day 1 and day 7, using McNemar test.

Comparison groups	Day 1 v Day 7
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage
Point estimate	67.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.9
upper limit	79.7

Primary: Change in a severity rating on a 7-point ordinal scale: day 28

End point title	Change in a severity rating on a 7-point ordinal scale: day 28

End point description:

Change in a severity rating on a 7-point ordinal scale:
1. Death
2. Hospitalised, on invasive mechanical ventilation or ECMO
3. Hospitalised, on non-invasive ventilation or high flow oxygen devices
4. Hospitalised, requiring supplemental oxygen
5. Hospitalised, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalised, not requiring supplemental oxygen – no longer requires ongoing medical care
7. Not hospitalised

End point type	Primary

End point timeframe:

Day 28

End point values	Day 1	Day 28		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	56		
Units: Subjects				
Severity 1	0	0		
Severity 2	1	1		
Severity 3	6	1		
Severity 4	37	1		
Severity 5	11	0		
Severity 6	0	0		
Severity 7	0	53		

Statistical analyses

Statistical analysis title	Patients who worsened

Statistical analysis description:

It was performed an analysis of contingency tables to see the evolution in 7-point ordinal severity score between day 1 and day 28, using McNemar test.

Comparison groups	Day 1 v Day 28
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	5.3

Statistical analysis title	Patients who remained stable

Statistical analysis description:

It was performed an analysis of contingency tables to see the evolution in 7-point ordinal severity score between day 1 and day 28, using McNemar test.

Comparison groups	Day 1 v Day 28

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Statistical analysis title	Patients who improved

Statistical analysis description:

It was performed an analysis of contingency tables to see the evolution in 7-point ordinal severity score between day 1 and day 28, using McNemar test.

Comparison groups	Day 1 v Day 28
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage
Point estimate	98.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	94.7
upper limit	100

Secondary: Percentage of patients reporting each severity rating on a 7-point severity ordinal scale

End point title	Percentage of patients reporting each severity rating on a 7-point severity ordinal scale

End point description:

7-point severity ordinal scale:
1. Death
2. Hospitalised, on invasive mechanical ventilation or ECMO
3. Hospitalised, on non-invasive ventilation or high flow oxygen devices
4. Hospitalised, requiring supplemental oxygen
5. Hospitalised, not requiring supplemental oxygen – requiring ongoing medical care (COVID-19 related or otherwise)
6. Hospitalised, not requiring supplemental oxygen – no longer requires ongoing medical care
7. Not hospitalised

End point type	Secondary

End point timeframe:

Day 7

End point values	Sarilumab			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: Subjects				
Severity 1	0			
Severity 2	1			
Severity 3	2			
Severity 4	13			
Severity 5	17			
Severity 6	20			
Severity 7	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of mechanical ventilation measured by days of ventilation since treatment

End point title	Duration of mechanical ventilation measured by days of ventilation since treatment

End point description:

"Duration of mechanical ventilation" is defined as: time from intubation date to extubation date (days)

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Sarilumab			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Days				
arithmetic mean (standard deviation)	8.7 (± 7.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of ventilator free days in the first 28 days

End point title	Number of ventilator free days in the first 28 days

End point description:

"Number of ventilator free days" is defined as: difference between 28 days and the duration with mechanical ventilation

End point type	Secondary

End point timeframe:

Baseline to day 28

End point values	Sarilumab			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: Days				
arithmetic mean (standard deviation)	20.4 (± 5.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients requiring mechanical ventilation

End point title	Number of patients requiring mechanical ventilation

End point description:

Patients with at least one oxygen requirement

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 1	Day 2	Day 3	Day 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	60	59	56
Units: Subjects				
No	12	21	19	17
Yes	48	39	40	39

End point values	Day 7	Day 28		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	56		
Units: Subjects				
No	37	52		
Yes	18	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients admitted to the ICU

End point title	Number of patients admitted to the ICU

End point description:

Patients with at least one entry in the intensive care unit (ICU)

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Sarilumab			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Subjects				
No	53			
Yes	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to resolution of fever without antipyretics for at least 48 hours (Tº > 36.6ºC – axilla; > 37.2ºC –oral; > 37.8 –rectal or tympanic)

End point title	Time to resolution of fever without antipyretics for at least 48 hours (Tº > 36.6ºC – axilla; > 37.2ºC –oral; > 37.8 –rectal or tympanic)

End point description:

The analysis is only performed for those patients whose first temperature measurement has been> 36.6ºC (method axilar)

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Sarilumab			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Days				
arithmetic mean (standard deviation)	1.5 (± 0.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in hemoglobin levels if available on day 2, 3, 4, 7, and 28

End point title	Changes from baseline in hemoglobin levels if available on day 2, 3, 4, 7, and 28

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	55	49	48
Units: g/dL				
arithmetic mean (standard deviation)	13.4 (± 1.2)	13.4 (± 1.2)	13.5 (± 1.1)	13.8 (± 1.5)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	60	55	49
Units: g/dL				
arithmetic mean (standard deviation)	13.9 (± 1.3)	13.6 (± 1.3)	13.6 (± 1.2)	13.6 (± 1.2)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	56		
Units: g/dL				
arithmetic mean (standard deviation)	13.6 (± 1.2)	13.6 (± 1.3)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the haemoglobin between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the haemoglobin between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the haemoglobin between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.552 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the haemoglobin between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.275 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the haemoglobin between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in platelet cell count if available on day 2, 3, 4, 7, and 28

End point title	Changes from baseline in platelet cell count if available on day 2, 3, 4, 7, and 28

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	55	49	48
Units: 10^9/L				
arithmetic mean (standard deviation)	257.0 (± 100.3)	282.2 (± 113.0)	322.2 (± 124.1)	360.1 (± 142.2)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	60	55	49
Units: 10^9/L				
arithmetic mean (standard deviation)	219.5 (± 86.0)	221.8 (± 79.4)	220.2 (± 78.6)	230.8 (± 80.7)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	56		
Units: 10^9/L				
arithmetic mean (standard deviation)	222.8 (± 81.5)	224.5 (± 80.1)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the platelet count between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the platelet count between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the platelet count between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the platelet count between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the platelet count between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.851 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - Since the p-value is over 0.05, there is no significant difference.

Secondary: Changes from baseline in D-Dimer leves if available on day 2, 3, 4, 7, and 28

End point title	Changes from baseline in D-Dimer leves if available on day 2, 3, 4, 7, and 28

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	53	48	47
Units: ng/mL				
arithmetic mean (standard deviation)	981.8 (± 821.9)	957.7 (± 1117.9)	1065.2 (± 1883.5)	933.8 (± 1180.6)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	52	57	53	48
Units: ng/mL				
arithmetic mean (standard deviation)	609.6 (± 1190.2)	936.3 (± 875.3)	917.9 (± 894.6)	858.5 (± 757.3)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	52		
Units: ng/mL				
arithmetic mean (standard deviation)	965.7 (± 940.4)	919.6 (± 900.7)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the D-dimer levels between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.469 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the D-dimer levels between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)

Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.896 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the D-dimer levels between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.975 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the D-dimer levels between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the D-dimer levels between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:
[15] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Number of deaths due to any cause

End point title	Number of deaths due to any cause

End point description:

End point type	Secondary

End point timeframe:
Up to day 28

End point values	Sarilumab			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Subjects				
Dead	1			
Not dead	59			

Statistical analyses

No statistical analyses for this end point

Secondary: Organ failure (DIC, cardiac, hepatic, renal, cardiovascular)

End point title	Organ failure (DIC, cardiac, hepatic, renal, cardiovascular)

End point description:
Brescia, SOFA / Sequential organ failure assessment (SOFA) score (In agreement with hospital protocol)

End point type	Secondary

End point timeframe:
Up to day 28

End point values	Day 1	Day 2	Day 3	Day 4
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	31	26	25	25
Units: Subjects				
0.	12	17	14	16
1.	15	6	3	1
2.	3	3	4	4
3.	0	0	3	3
4.	0	0	1	0
5.	1	0	0	1

End point values	Day 7	Day 28		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	17		
Units: Subjects				
0.	14	16		
1.	4	0		
2.	2	0		
3.	1	0		
4.	0	1		
5.	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: C-Reactive Protein (CRP)

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: C-Reactive Protein (CRP)

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	54	49	47
Units: mg/dL				
arithmetic mean (standard deviation)	12.2 (± 21.1)	4.3 (± 4.6)	2.4 (± 2.6)	1.7 (± 7.5)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	55	57	54	49
Units: mg/dL				
arithmetic mean (standard deviation)	1.2 (± 3.2)	19.1 (± 40.3)	19.4 (± 41.4)	20.0 (± 43.2)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	55		
Units: mg/dL				
arithmetic mean (standard deviation)	21.5 (± 44.0)	18.7 (± 40.3)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the CRP between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the CRP between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the CRP between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the CRP between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the CRP between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Lactate dehydrogenase (LDH)

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Lactate dehydrogenase (LDH)

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	51	45	45
Units: UI/L				
arithmetic mean (standard deviation)	387.5 (± 128.9)	397.0 (± 144.6)	375.9 (± 135.8)	346.8 (± 132.9)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	54	51	45
Units: UI/L				
arithmetic mean (standard deviation)	271.0 (± 75.4)	373.8 (± 119.1)	370.1 (± 121.6)	360.7 (± 119.0)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	45	50		
Units: UI/L				
arithmetic mean (standard deviation)	382.1 (± 127.1)	365.9 (± 97.0)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the LDH between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the LDH between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the LDH between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.087 [23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the LDH between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the LDH between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: serum ferritin

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: serum ferritin

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	52	48	44	42
Units: ng/mL				
arithmetic mean (standard deviation)	1489.2 (± 873.9)	1332.1 (± 791.8)	1205.5 (± 729.5)	1065.6 (± 879.8)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	52	48	44
Units: ng/mL				
arithmetic mean (standard deviation)	457.1 (± 269.2)	1328.9 (± 773.5)	1256.9 (± 753.3)	1332.9 (± 773.4)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	50		
Units: ng/mL				
arithmetic mean (standard deviation)	1355.4 (± 836.6)	1289.9 (± 815.5)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the ferritin between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.

In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the ferritin between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.454 [27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the ferritin between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the ferritin between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)

Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [29]
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the ferritin between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [30]
Method	Wilcoxon (Mann-Whitney)

Notes:

[30] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Troponin

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Troponin

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	13	15	12
Units: ng/L				
arithmetic mean (standard deviation)	8.9 (± 14.8)	6.8 (± 9.5)	9.7 (± 12.2)	4.9 (± 9.4)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	14	13	15
Units: ng/L				
arithmetic mean (standard deviation)	6.2 (± 10.3)	9.4 (± 15.8)	7.4 (± 10.0)	11.7 (± 15.5)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	13		
Units: ng/L				
arithmetic mean (standard deviation)	4.9 (± 9.1)	6.2 (± 10.1)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the troponin between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273 [31]
Method	Wilcoxon (Mann-Whitney)

Notes:

[31] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the troponin between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.144 [32]
Method	Wilcoxon (Mann-Whitney)

Notes:

[32] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the troponin between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [33]
Method	Wilcoxon (Mann-Whitney)

Notes:

[33] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the troponin between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.655 [34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[34] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the troponin between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999 [35]
Method	Wilcoxon (Mann-Whitney)

Notes:

[35] - Since the p-value is over 0.05, there is no significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Blood Urea Nitrogen (BUN)

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Blood Urea Nitrogen (BUN)

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	52	42	40
Units: mg/dL				
arithmetic mean (standard deviation)	36.5 (± 21.5)	37.2 (± 21.6)	37.5 (± 24.3)	38.7 (± 26.0)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	58	52	42
Units: mg/dL				
arithmetic mean (standard deviation)	32.2 (± 19.7)	33.9 (± 20.0)	33.2 (± 20.7)	33.0 (± 22.3)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	54		
Units: mg/dL				
arithmetic mean (standard deviation)	34.2 (± 23.2)	33.7 (± 20.7)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the BUN between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [36]
Method	Wilcoxon (Mann-Whitney)

Notes:

[36] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the BUN between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [37]
Method	Wilcoxon (Mann-Whitney)

Notes:

[37] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the BUN between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [38]
Method	Wilcoxon (Mann-Whitney)

Notes:

[38] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the BUN between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019 [39]
Method	Wilcoxon (Mann-Whitney)

Notes:

[39] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the BUN between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.515 [40]
Method	Wilcoxon (Mann-Whitney)

Notes:

[40] - Since the p-value is over 0.05, there is no significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: creatinine

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: creatinine

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	52	45	43
Units: mg/dL				
arithmetic mean (standard deviation)	0.88 (± 0.27)	0.84 (± 0.23)	0.86 (± 0.24)	0.87 (± 0.26)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	53	58	52	45
Units: mg/dL				
arithmetic mean (standard deviation)	0.88 (± 0.29)	0.89 (± 0.26)	0.87 (± 0.23)	0.88 (± 0.24)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	53		
Units: mg/dL				
arithmetic mean (standard deviation)	0.90 (± 0.27)	0.91 (± 0.26)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the cretinine between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.206 [41]
Method	Wilcoxon (Mann-Whitney)

Notes:

[41] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the cretinine between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [42]
Method	Wilcoxon (Mann-Whitney)

Notes:

[42] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4
Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.287 [43]
Method	Wilcoxon (Mann-Whitney)

Notes:

[43] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the cretinine between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07 [44]
Method	Wilcoxon (Mann-Whitney)

Notes:

[44] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the cretinine between day 1 and day 28, the Wilcoxon test was used

with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.192 [45]
Method	Wilcoxon (Mann-Whitney)

Notes:

[45] - Since the p-value is over 0.05, there is no significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Aspartate Transaminase (AST)

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Aspartate Transaminase (AST)

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	34	30	32
Units: UI/L				
arithmetic mean (standard deviation)	55.2 (± 34.6)	69.5 (± 67.9)	71.0 (± 51.2)	56.0 (± 51.3)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	46	34	30
Units: UI/L				
arithmetic mean (standard deviation)	32.4 (± 20.0)	49.2 (± 28.1)	53.2 (± 27.8)	46.6 (± 18.3)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	50		
Units: UI/L				
arithmetic mean (standard deviation)	57.0 (± 31.0)	50.3 (± 28.9)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the AST between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 1 (N = N Day 2) v Day 2
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [46]
Method	Wilcoxon (Mann-Whitney)

Notes:

[46] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the AST between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.347 [47]
Method	Wilcoxon (Mann-Whitney)

Notes:

[47] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the AST between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [48]
Method	Wilcoxon (Mann-Whitney)

Notes:

[48] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the AST between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83 [49]
Method	Wilcoxon (Mann-Whitney)

Notes:

[49] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the AST between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [50]
Method	Wilcoxon (Mann-Whitney)

Notes:

[50] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Alanine Transaminase (ALT)

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: Alanine Transaminase (ALT)

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	35	31	33
Units: UI/L				
arithmetic mean (standard deviation)	69.9 (± 61.3)	94.5 (± 88.9)	116.9 (± 111.3)	164.5 (± 178.1)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	51	47	35	31
Units: UI/L				
arithmetic mean (standard deviation)	68.2 (± 51.9)	56.0 (± 44.2)	60.5 (± 45.1)	53.0 (± 33.7)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	51		
Units: UI/L				
arithmetic mean (standard deviation)	70.0 (± 46.6)	56.4 (± 44.9)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the ALT between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [51]
Method	Wilcoxon (Mann-Whitney)

Notes:

[51] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the ALT between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [52]
Method	Wilcoxon (Mann-Whitney)

Notes:

[52] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the ALT between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [53]
Method	Wilcoxon (Mann-Whitney)

Notes:

[53] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the ALT between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [54]
Method	Wilcoxon (Mann-Whitney)

Notes:

[54] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the ALT between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.135 [55]
Method	Wilcoxon (Mann-Whitney)

Notes:

[55] - Since the p-value is over 0.05, there is no significant difference.

Secondary: Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: total bilirrubin

End point title	Changes from baseline in inflammatory parameters and other laboratory tests available on day 2, 3, 4, 7, and 28: total bilirrubin

End point description:

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	43	37	36	38
Units: mg/dL				
arithmetic mean (standard deviation)	0.32 (± 0.1)	0.33 (± 0.13)	0.33 (± 0.13)	0.40 (± 0.13)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	47	43	37	36
Units: mg/dL				
arithmetic mean (standard deviation)	0.54 (± 0.19)	0.41 (± 0.2)	0.46 (± 0.23)	0.43 (± 0.23)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	47		
Units: mg/dL				
arithmetic mean (standard deviation)	0.45 (± 0.23)	0.42 (± 0.22)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the total bilirrubin between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 1 (N = N Day 2) v Day 2

Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [56]
Method	Wilcoxon (Mann-Whitney)

Notes:

[56] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the total bilirrubin between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [57]
Method	Wilcoxon (Mann-Whitney)

Notes:

[57] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the total bilirrubin between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [58]
Method	Wilcoxon (Mann-Whitney)

Notes:

[58] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the total bilirrubin between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.238 [59]
Method	Wilcoxon (Mann-Whitney)

Notes:

[59] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the total bilirrubin between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [60]
Method	Wilcoxon (Mann-Whitney)

Notes:

[60] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: leucocytes

End point title	Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: leucocytes

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	55	49	48
Units: 10^9/L				
arithmetic mean (standard deviation)	6.2 (± 4.0)	6.6 (± 3.6)	6.8 (± 2.8)	8.8 (± 4.5)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	60	55	49
Units: 10^9/L				
arithmetic mean (standard deviation)	6.5 (± 2.4)	7.5 (± 3.1)	7.7 (± 3.2)	7.7 (± 3.1)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		

Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	56		
Units: 10^9/L				
arithmetic mean (standard deviation)	8.0 (± 3.2)	7.8 (± 3.1)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the leucocytes between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [61]
Method	Wilcoxon (Mann-Whitney)

Notes:

[61] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the leucocytes between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021 [62]
Method	Wilcoxon (Mann-Whitney)

Notes:

[62] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4
Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [63]
Method	Wilcoxon (Mann-Whitney)

Notes:

[63] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the leucocytes between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.298 [64]
Method	Wilcoxon (Mann-Whitney)

Notes:

[64] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the leucocytes between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [65]
Method	Wilcoxon (Mann-Whitney)

Notes:

[65] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: neutrophils

End point title	Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: neutrophils

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	55	49	48
Units: 10^9/L				
arithmetic mean (standard deviation)	4.7 (± 4.0)	4.9 (± 3.5)	4.9 (± 2.6)	6.2 (± 4.1)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)

Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	60	55	49
Units: 10^9/L				
arithmetic mean (standard deviation)	3.9 (± 2.3)	6.0 (± 3.2)	6.1 (± 3.3)	6.2 (± 3.2)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	56		
Units: 10^9/L				
arithmetic mean (standard deviation)	6.5 (± 3.3)	6.2 (± 3.2)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the neutrophils between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [66]
Method	Wilcoxon (Mann-Whitney)

Notes:

[66] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the neutrophils between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [67]
Method	Wilcoxon (Mann-Whitney)

Notes:

[67] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the neutrophils between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.

In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [68]
Method	Wilcoxon (Mann-Whitney)

Notes:

[68] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the neutrophils between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.462 [69]
Method	Wilcoxon (Mann-Whitney)

Notes:

[69] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the neutrophils between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [70]
Method	Wilcoxon (Mann-Whitney)

Notes:

[70] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: linfocytes

End point title	Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: linfocytes

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	55	49	48
Units: 10^9/L				
arithmetic mean (standard deviation)	1.1 (± 0.4)	1.2 (± 0.5)	1.3 (± 0.6)	1.8 (± 0.8)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	60	55	49
Units: 10^9/L				
arithmetic mean (standard deviation)	1.8 (± 0.6)	1.1 (± 0.4)	1.0 (± 0.4)	1.0 (± 0.4)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	56		
Units: 10^9/L				
arithmetic mean (standard deviation)	1.0 (± 0.4)	1.0 (± 0.5)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the linfocytes between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.956 [71]
Method	Wilcoxon (Mann-Whitney)

Notes:

[71] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the linfocytes between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.

In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [72]
Method	Wilcoxon (Mann-Whitney)

Notes:

[72] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the linfocytes between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [73]
Method	Wilcoxon (Mann-Whitney)

Notes:

[73] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the linfocytes between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [74]
Method	Wilcoxon (Mann-Whitney)

Notes:

[74] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the linfocytes between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)

Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [75]
Method	Wilcoxon (Mann-Whitney)

Notes:

[75] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: monocytes

End point title	Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: monocytes

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	55	49	48
Units: 10^9/L				
arithmetic mean (standard deviation)	0.38 (± 0.21)	0.42 (± 0.22)	0.46 (± 0.25)	0.61 (± 0.26)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	60	55	49
Units: 10^9/L				
arithmetic mean (standard deviation)	0.60 (± 0.23)	0.43 (± 0.21)	0.42 (± 0.21)	0.43 (± 0.22)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48	56		
Units: 10^9/L				
arithmetic mean (standard deviation)	0.42 (± 0.21)	0.42 (± 0.21)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the monocytes between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [76]
Method	Wilcoxon (Mann-Whitney)

Notes:

[76] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the monocytes between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556 [77]
Method	Wilcoxon (Mann-Whitney)

Notes:

[77] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the monocytes between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.511 [78]
Method	Wilcoxon (Mann-Whitney)

Notes:

[78] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the monocytes between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [79]
Method	Wilcoxon (Mann-Whitney)

Notes:

[79] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the monocytes between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [80]
Method	Wilcoxon (Mann-Whitney)

Notes:

[80] - Since the p-value is under 0.05, there is a significant difference.

Secondary: Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: eosinophils

End point title	Changes from baseline in white blood cell count if available on day 2, 3, 4, 7, and 28: eosinophils

End point description:

End point type	Secondary

End point timeframe:

Up to 28 days or discharge

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	15	13	12
Units: 10^9/L				
arithmetic mean (standard deviation)	0.05 (± 0.05)	0.04 (± 0.05)	0.09 (± 0.07)	0.06 (± 0.05)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	20	17	15	13
Units: 10^9/L				
arithmetic mean (standard deviation)	0.15 (± 0.10)	0.07 (± 0.09)	0.07 (± 0.09)	0.08 (± 0.10)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	20		
Units: 10^9/L				
arithmetic mean (standard deviation)	0.08 (± 0.10)	0.06 (± 0.08)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the eosinophils between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 1 (N = N Day 2) v Day 2
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.859 [81]
Method	Wilcoxon (Mann-Whitney)

Notes:

[81] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the eosinophils between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.789 [82]
Method	Wilcoxon (Mann-Whitney)

Notes:

[82] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the eosinophils between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)

Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.386 [83]
Method	Wilcoxon (Mann-Whitney)

Notes:

[83] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the eosinophils between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.965 [84]
Method	Wilcoxon (Mann-Whitney)

Notes:

[84] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the eosinophils between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012 [85]
Method	Wilcoxon (Mann-Whitney)

Notes:

[85] - Since the p-value is under 0.05, there is a significant difference.

Other pre-specified: Change from baseline of cytokine levels associated with the cytokine storm, including, among others, IL-6 on day 1 vs any other determination done up to day 28

End point title	Change from baseline of cytokine levels associated with the cytokine storm, including, among others, IL-6 on day 1 vs any other determination done up to day 28

End point description:

End point type	Other pre-specified

End point timeframe:

Up to day 28

End point values	Day 2	Day 3	Day 4	Day 7
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	30	29	29
Units: g/mL				
arithmetic mean (standard deviation)	399.4 (± 572.2)	352.3 (± 503.3)	382.2 (± 612.3)	165.7 (± 299.7)

End point values	Day 28	Day 1 (N = N Day 2)	Day 1 (N = N Day 3)	Day 1 (N = N day 4)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	24	32	30	29
Units: g/mL				
arithmetic mean (standard deviation)	21.5 (± 35.7)	33.2 (± 23.4)	36.9 (± 27.6)	37.4 (± 28.7)

End point values	Day 1 (N = N Day 7)	Day 1 (N = N Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	24		
Units: g/mL				
arithmetic mean (standard deviation)	35.5 (± 26.7)	29.4 (± 21.1)		

Statistical analyses

Statistical analysis title	Day 1 vs day 2

Statistical analysis description:

In order to observe the evolution of the IL-6 levels between day 1 and day 2, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 2 v Day 1 (N = N Day 2)
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [86]
Method	Wilcoxon (Mann-Whitney)

Notes:

[86] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 3

Statistical analysis description:

In order to observe the evolution of the IL-6 levels between day 1 and day 3, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 3 v Day 1 (N = N Day 3)

Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [87]
Method	Wilcoxon (Mann-Whitney)

Notes:

[87] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 4

Statistical analysis description:

In order to observe the evolution of the IL-6 levels between day 1 and day 4, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 4 v Day 1 (N = N day 4)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [88]
Method	Wilcoxon (Mann-Whitney)

Notes:

[88] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 7

Statistical analysis description:

In order to observe the evolution of the IL-6 levels between day 1 and day 7, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 7 v Day 1 (N = N Day 7)
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [89]
Method	Wilcoxon (Mann-Whitney)

Notes:

[89] - Since the p-value is under 0.05, there is a significant difference.

Statistical analysis title	Day 1 vs day 28

Statistical analysis description:

In order to observe the evolution of the IL-6 levels between day 1 and day 28, the Wilcoxon test was used with a significance level of 0.05.
In cases where a p-value less than 0.05 appear, it refers to the existence of statistical significance.

Comparison groups	Day 28 v Day 1 (N = N Day 28)
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [90]
Method	Wilcoxon (Mann-Whitney)

Notes:
[90] - Since the p-value is under 0.05, there is a significant difference.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the duration of the trial	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	Sarilumab
Reporting group description: Treatment of severe COVID-19 with sarilumab	

Serious adverse events	Sarilumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 60 (30.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Sarilumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 60 (45.00%)		
Vascular disorders			
Cyanosis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Condition aggravated subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
General physical health deterioration subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Pyrexia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3		
Dyspnoea subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Hypoxia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Rales subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Use of accessory respiratory muscles subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Delirium subjects affected / exposed occurrences (all)	2 / 60 (3.33%) 2		
Depression			

subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Blood pressure decreased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Fibrin D dimer increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Hypophonesis			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Interleukin level increased			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Oxygen saturation decreased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Serum ferritin decreased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Serum ferritin increased			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences (all)	2		
Transaminases increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Conduction disorder			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences (all)	1		
Neutropenia			

subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1 1 / 60 (1.67%) 1		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Odynophagia subjects affected / exposed occurrences (all)	 3 / 60 (5.00%) 3 2 / 60 (3.33%) 2 1 / 60 (1.67%) 1 1 / 60 (1.67%) 1		
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1		
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1 1 / 60 (1.67%) 1		
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1		

Pneumonia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypernatraemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Malnutrition subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1 1 / 60 (1.67%) 1 1 / 60 (1.67%) 1 1 / 60 (1.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2020	Deletion of Exclusion criterion 7 (use of corticosteroids) and exclusion criterion 18 (positive serology for HIV, Hepatitis B and C).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study is limited by the absence of a control group, so data must be interpreted with caution. However, judging from contemporary registries, mortality in the study was below that expected for the patient population.

Notes:

Online references

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