



Clinical trial results:

A multicentre, open-label clinical trial to evaluate the effectiveness and safety of intravenous tocilizumab for treating patients with COVID-19 pneumonia: the BREATH-19 Study

Summary

EudraCT number	2020-001995-13
Trial protocol	ES
Global end of trial date	17 June 2022

Results information

Result version number	v1 (current)
This version publication date	12 April 2026
First version publication date	12 April 2026
Summary attachment (see zip file)	BREATH-19_SUMMARY (BREATH-19_SUMMARY.pdf)

Trial information

Trial identification

Sponsor protocol code	BREATH-19
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	FSG011-20: FSG011-20

Notes:

Sponsors

Sponsor organisation name	Fundación SEIMC-GeSIDA
Sponsor organisation address	Agustín de Betancourt, 13, Madrid, Spain, 29003
Public contact	Raúl Montalbán Casado, Dynamic Science S.L., 0034 91 456 11 05, raul.m@dynasolutions.com
Scientific contact	Raúl Montalbán Casado, Dynamic Science S.L., 0034 91 456 11 05, raul.m@dynasolutions.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 June 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study are evaluated in both the overall and retrospective cohorts.

The main objective is to evaluate the effectiveness of IV tocilizumab in treating patients with COVID-19 pneumonia by describing the:

- Improvement of respiratory function based on:
 - Time to intubation (if not previously intubated) and duration of intubation.
 - Time of non-invasive mechanical ventilation.
 - Time of oxygen therapy.
- Mortality rate

Protection of trial subjects:

In this study, patients were closely monitored for the development of signs and symptoms of infection during and after treatment with tocilizumab. The risk to subjects in this trial was minimized by compliance with the inclusion/exclusion criteria, close clinical monitoring, and minimal study duration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 444
Worldwide total number of subjects	444
EEA total number of subjects	444

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	235
From 65 to 84 years	209
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were included in the study between May 14th, 2020, and November 23rd, 2020.

Pre-assignment

Screening details:

According to the inclusion criteria, patients could be included prospectively and retrospectively. A total of 462 patients were initially included in the database; however, 18 were screening failures. Therefore, the evaluable population included 444 patients, with 247 enrolled retrospectively and 197 enrolled prospectively.

Period 1

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

Arms

Arm title	Tocilizumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients will receive IV tocilizumab as per clinical practice and at the discretion of the treating investigator, following the posology indicated in the SmPC or the recommendations proposed by the Spanish Ministry of Health:

o The SmPC:

The recommended posology for treatment of Cytokine storm syndrome (CSS) given as a 60-minute IV infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. If no clinical improvement in the signs and symptoms of CSS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CSS patients.

o The recommendations of the Spanish Ministry of Health:

Patients \geq 80 kg: first dose 600 mg; second dose 600 mg.

Patients < 80 kg: first dose 600 mg; second dose 400 mg.

Number of subjects in period 1	Tocilizumab
Started	444
Completed	444

Period 2

Period 2 title	Visit 1 / Screening
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tocilizumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients will receive IV tocilizumab as per clinical practice and at the discretion of the treating investigator, following the posology indicated in the SmPC or the recommendations proposed by the Spanish Ministry of Health:

o The SmPC:

The recommended posology for treatment of Cytokine storm syndrome (CSS) given as a 60-minute IV infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. If no clinical improvement in the signs and symptoms of CSS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CSS patients.

o The recommendations of the Spanish Ministry of Health:

Patients \geq 80 kg: first dose 600 mg; second dose 600 mg.

Patients < 80 kg: first dose 600 mg; second dose 400 mg.

Number of subjects in period 2	Tocilizumab
Started	444
Completed	444

Period 3

Period 3 title	Last available visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Tocilizumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients will receive IV tocilizumab as per clinical practice and at the discretion of the treating investigator, following the posology indicated in the SmPC or the recommendations proposed by the Spanish Ministry of Health:

o The SmPC:

The recommended posology for treatment of Cytokine storm syndrome (CSS) given as a 60-minute IV infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. If no clinical improvement in the signs and symptoms of CSS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CSS patients.

o The recommendations of the Spanish Ministry of Health:

Patients \geq 80 kg: first dose 600 mg; second dose 600 mg.

Patients < 80 kg: first dose 600 mg; second dose 400 mg.

Arm title	Single-dose
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients will receive IV tocilizumab as per clinical practice and at the discretion of the treating investigator, following the posology indicated in the SmPC or the recommendations proposed by the Spanish Ministry of Health:

o The SmPC:

The recommended posology for treatment of Cytokine storm syndrome (CSS) given as a 60-minute IV infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. If no clinical improvement in the signs and symptoms of CSS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CSS patients.

o The recommendations of the Spanish Ministry of Health:

Patients \geq 80 kg: first dose 600 mg; second dose 600 mg.

Patients < 80 kg: first dose 600 mg; second dose 400 mg.

Arm title	Multiple-dose
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients will receive IV tocilizumab as per clinical practice and at the discretion of the treating investigator, following the posology indicated in the SmPC or the recommendations proposed by the Spanish Ministry of Health:

o The SmPC:

The recommended posology for treatment of Cytokine storm syndrome (CSS) given as a 60-minute IV infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. If no clinical improvement in the signs and symptoms of CSS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses

should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CSS patients.

- o The recommendations of the Spanish Ministry of Health:
Patients \geq 80 kg: first dose 600 mg; second dose 600 mg.
Patients < 80 kg: first dose 600 mg; second dose 400 mg.

Number of subjects in period 3	Tocilizumab	Single-dose	Multiple-dose
Started	444	337	107
Completed	444	337	107

Period 4

Period 4 title	End of study visit
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Tocilizumab
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Patients will receive IV tocilizumab as per clinical practice and at the discretion of the treating investigator, following the posology indicated in the SmPC or the recommendations proposed by the Spanish Ministry of Health:

- o The SmPC:

The recommended posology for treatment of Cytokine storm syndrome (CSS) given as a 60-minute IV infusion is 8 mg/kg in patients weighing greater than or equal to 30 kg or 12 mg/kg in patients weighing less than 30 kg. If no clinical improvement in the signs and symptoms of CSS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses should be at least 8 hours. Doses exceeding 800 mg per infusion are not recommended in CSS patients.

- o The recommendations of the Spanish Ministry of Health:

Patients \geq 80 kg: first dose 600 mg; second dose 600 mg.

Patients < 80 kg: first dose 600 mg; second dose 400 mg.

Number of subjects in period 4	Tocilizumab
Started	444
Completed	444

Baseline characteristics

Reporting groups

Reporting group title	Tocilizumab
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Reporting group description: -

Reporting group values	Tocilizumab	Total	
Number of subjects	444	444	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	63.6		
standard deviation	± 14.8	-	
Gender categorical			
Units: Subjects			
Female	137	137	
Male	307	307	
RT-PCR			
Units: Subjects			
Positive	444	444	
Severity			
Units: Subjects			
Mild (early infection)	13	13	
Moderate (pulmonary involvement without hypoxia)	157	157	
Severe (systematic hyper-inflammation)	251	251	
Critical (multiple organ dysfunction syndrome)	22	22	
Unknown	1	1	
Chest X-ray / CT-scan performed			
Units: Subjects			
Yes	438	438	
No	6	6	
Type of test			
Units: Subjects			
X-ray	405	405	
CT-scan	33	33	

Missing	6	6	
Test result			
Units: Subjects			
Normal	3	3	
Abnormal	435	435	
Unknown	6	6	
Hospitalization / ICU			
Units: Subjects			
Hospitalization	404	404	
ICU	40	40	
Cytokine storm syndrome (CSS) development			
Units: Subjects			
Yes	364	364	
No	80	80	
Number of combined therapies			
Units: Subjects			
One	10	10	
Two	19	19	
Three	37	37	
Four	40	40	
Five	41	41	
Six	54	54	
Seven	33	33	
Eight	37	37	
Nine	25	25	
Ten or more	147	147	
Zero	1	1	
Respiratory rate			
Units: bpm			
arithmetic mean	23.6		
standard deviation	± 6.0	-	
PaO2			
Units: mmHg			
arithmetic mean	64.0		
standard deviation	± 15.1	-	
Time from onset of symptoms to the first dose of tocilizumab			
Units: days			
arithmetic mean	10.3		
standard deviation	± 6.5	-	
Time from CSS to the first dose of tocilizumab			
Units: days			
arithmetic mean	1.3		
standard deviation	± 3.0	-	
Systolic blood pressure			
Units: mmHg			
arithmetic mean	125.9		
standard deviation	± 18.1	-	
Diastolic blood pressure			
Units: mmHg			

arithmetic mean	73.3		
standard deviation	± 11.1	-	
Heart rate			
Units: bpm			
arithmetic mean	82.6		
standard deviation	± 17.0	-	
Body temperature			
Units: °C			
arithmetic mean	36.8		
standard deviation	± 1.0	-	

Subject analysis sets

Subject analysis set title	Retrospective cohort (baseline characteristics)
Subject analysis set type	Full analysis

Subject analysis set description:

This subject analysis set has been created solely for posting results related to the baseline characteristics of the retrospective subcohort.

Subject analysis set title	Retrospective cohort at screening/visit 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set was created to report results related to the retrospective subcohort at Screening/Visit 1, when applicable.

Subject analysis set title	Retrospective cohort at last visit available
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set was created to report results related to the retrospective subcohort at last visit available, when applicable.

Subject analysis set title	Retrospective cohort (single dose)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set was created to report results related to the retrospective subcohort with single dose of tocilizumab, when applicable.

Subject analysis set title	Retrospective cohort (multiple doses)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

This subject analysis set was created to report results related to the retrospective subcohort with multiple doses of tocilizumab, when applicable.

Reporting group values	Retrospective cohort (baseline characteristics)	Retrospective cohort at screening/visit 1	Retrospective cohort at last visit available
Number of subjects	247	247	247
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			

85 years and over			
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Age continuous Units: years arithmetic mean standard deviation	63.5 ± 14.2	±	±
Gender categorical Units: Subjects			
Female	77		
Male	170		
RT-PCR Units: Subjects			
Positive	247		
Severity Units: Subjects			
Mild (early infection)	9		
Moderate (pulmonary involvement without hypoxia)	93		
Severe (systematic hyper-inflammation)	125		
Critical (multiple organ dysfunction syndrome)	19		
Unknown	1		
Chest X-ray / CT-scan performed Units: Subjects			
Yes	241		
No	6		
Type of test Units: Subjects			
X-ray	224		
CT-scan	17		
Missing	6		
Test result Units: Subjects			
Normal	1		
Abnormal	240		
Unknown	6		
Hospitalization / ICU Units: Subjects			
Hospitalization	212		
ICU	35		
Cytokine storm syndrome (CSS) development Units: Subjects			
Yes	194		
No	53		
Number of combined therapies Units: Subjects			
One	6		
Two	8		
Three	19		

Four	26		
Five	21		
Six	31		
Seven	22		
Eight	17		
Nine	15		
Ten or more	81		
Zero	1		
Respiratory rate Units: bpm arithmetic mean standard deviation	22.7 ± 5.8	±	±
PaO2 Units: mmHg arithmetic mean standard deviation	63.4 ± 15.5	±	±
Time from onset of symptoms to the first dose of tocilizumab Units: days arithmetic mean standard deviation	11.3 ± 7.5	±	±
Time from CSS to the first dose of tocilizumab Units: days arithmetic mean standard deviation	1.8 ± 3.8	±	±
Systolic blood pressure Units: mmHg arithmetic mean standard deviation	124.9 ± 18.9	±	±
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	72.7 ± 11.5	±	±
Heart rate Units: bpm arithmetic mean standard deviation	85.1 ± 18.0	±	±
Body temperature Units: °C arithmetic mean standard deviation	36.8 ± 1.0	±	±

Reporting group values	Retrospective cohort (single dose)	Retrospective cohort (multiple doses)	
Number of subjects	194	53	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	
Gender categorical Units: Subjects			
Female Male			
RT-PCR Units: Subjects			
Positive			
Severity Units: Subjects			
Mild (early infection) Moderate (pulmonary involvement without hypoxia) Severe (systematic hyper-inflammation) Critical (multiple organ dysfunction syndrome) Unknown			
Chest X-ray / CT-scan performed Units: Subjects			
Yes No			
Type of test Units: Subjects			
X-ray CT-scan Missing			
Test result Units: Subjects			
Normal Abnormal Unknown			
Hospitalization / ICU Units: Subjects			
Hospitalization ICU			
Cytokine storm syndrome (CSS) development Units: Subjects			
Yes No			
Number of combined therapies Units: Subjects			

One			
Two			
Three			
Four			
Five			
Six			
Seven			
Eight			
Nine			
Ten or more			
Zero			
Respiratory rate Units: bpm arithmetic mean standard deviation	\pm	\pm	
PaO2 Units: mmHg arithmetic mean standard deviation	\pm	\pm	
Time from onset of symptoms to the first dose of tocilizumab Units: days arithmetic mean standard deviation	\pm	\pm	
Time from CSS to the first dose of tocilizumab Units: days arithmetic mean standard deviation	\pm	\pm	
Systolic blood pressure Units: mmHg arithmetic mean standard deviation	\pm	\pm	
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	\pm	\pm	
Heart rate Units: bpm arithmetic mean standard deviation	\pm	\pm	
Body temperature Units: °C arithmetic mean standard deviation	\pm	\pm	

End points

End points reporting groups

Reporting group title	Tocilizumab
Reporting group description: -	
Reporting group title	Tocilizumab
Reporting group description: -	
Reporting group title	Tocilizumab
Reporting group description: -	
Reporting group title	Single-dose
Reporting group description: -	
Reporting group title	Multiple-dose
Reporting group description: -	
Reporting group title	Tocilizumab
Reporting group description: -	
Subject analysis set title	Retrospective cohort (baseline characteristics)
Subject analysis set type	Full analysis
Subject analysis set description: This subject analysis set has been created solely for posting results related to the baseline characteristics of the retrospective subcohort.	
Subject analysis set title	Retrospective cohort at screening/visit 1
Subject analysis set type	Sub-group analysis
Subject analysis set description: This subject analysis set was created to report results related to the retrospective subcohort at Screening/Visit 1, when applicable.	
Subject analysis set title	Retrospective cohort at last visit available
Subject analysis set type	Sub-group analysis
Subject analysis set description: This subject analysis set was created to report results related to the retrospective subcohort at last visit available, when applicable.	
Subject analysis set title	Retrospective cohort (single dose)
Subject analysis set type	Sub-group analysis
Subject analysis set description: This subject analysis set was created to report results related to the retrospective subcohort with single dose of tocilizumab, when applicable.	
Subject analysis set title	Retrospective cohort (multiple doses)
Subject analysis set type	Sub-group analysis
Subject analysis set description: This subject analysis set was created to report results related to the retrospective subcohort with multiple doses of tocilizumab, when applicable.	

Primary: Respiratory function

End point title	Respiratory function
End point description:	
End point type	Primary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Tocilizumab	Tocilizumab	Retrospective cohort at last visit available	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	444	444	247	
Units: days				
arithmetic mean (standard deviation)				
Time to intubation	2.8 (± 4.6)	2.8 (± 4.6)	3.1 (± 5.6)	
Duration of intubation	17.4 (± 15.2)	17.4 (± 15.2)	16.6 (± 15.1)	
Duration of intubation in tocilizumab	18.7 (± 15.7)	18.7 (± 15.7)	17.6 (± 15.6)	
Time to NIMV	2.2 (± 5.0)	2.2 (± 5.0)	2.8 (± 5.0)	
Duration of NIMV	8.8 (± 8.2)	8.8 (± 8.2)	10.8 (± 10.4)	
Duration of NIMV in tocilizumab	9.4 (± 9.4)	9.4 (± 9.4)	10.9 (± 12.2)	
Time to oxygen therapy	3.8 (± 8.4)	3.8 (± 8.4)	3.8 (± 8.4)	
Duration of oxygen therapy	9.2 (± 10.1)	9.2 (± 10.1)	11.6 (± 12.3)	
Duration of oxygen therapy in tocilizumab	8.6 (± 10.9)	8.6 (± 10.9)	10.9 (± 12.9)	

Statistical analyses

Statistical analysis title	Primary endpoint: improvement respiratory function
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	888
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Descriptive analysis
Parameter estimate	NA
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Primary: Mortality

End point title	Mortality
End point description:	
End point type	Primary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Tocilizumab	Tocilizumab	Retrospective cohort at last visit available	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	444	444	247	
Units: Percentage				
number (not applicable)	19.6	19.6	22.7	

Attachments (see zip file)	KM Overall survival (Primary endpoint for overall population). KM Overall survival (Primary endpoint for retrospective
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Statistical analyses

Statistical analysis title	Primary endpoint: mortality rate
Statistical analysis description:	
A descriptive statistical analysis was performed. Quantitative variables were described using measures of central tendency and dispersion. Qualitative variables were described using absolute frequencies and percentages. The 95% confidence intervals for these estimations were calculated.	
Comparison groups	Tocilizumab v Tocilizumab
Number of subjects included in analysis	888
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Descriptive analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0
Variability estimate	Standard deviation
Dispersion value	0

Secondary: Oxygenation parameters: SaO2

End point title	Oxygenation parameters: SaO2
End point description:	
End point type	Secondary
End point timeframe:	
At 1 day after the first dose and every 3 days during the hospitalization	

End point values	Tocilizumab	Retrospective cohort at last visit available		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	438	242		
Units: Percentage				
arithmetic mean (standard deviation)				
SaO2	93.1 (± 4.8)	92.7 (± 5.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Oxygenation parameters: PaFi (SaFi)

End point title	Oxygenation parameters: PaFi (SaFi)
End point description:	
End point type	Secondary
End point timeframe:	
At 1 day after the first dose and every 3 days during the hospitalization	

End point values	Tocilizumab	Retrospective cohort at last visit available		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	353	181		
Units: Subjects				
number (not applicable)				
≥ 300	99	61		
< 300	254	120		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of hospitalization

End point title	Duration of hospitalization
End point description:	
End point type	Secondary
End point timeframe:	
At 1 day after the first dose and every 3 days during the hospitalization	

End point values	Tocilizumab	Retrospective cohort at last visit available		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	444	247		
Units: days				
arithmetic mean (standard deviation)				
Time of hospitalization	20.9 (± 24.8)	23.3 (± 30.2)		
Time of hospitalization from the start of tocilizu	15.6 (± 15.2)	16.5 (± 15.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of intensive care unit stay

End point title	Duration of intensive care unit stay
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End point description:

End point type	Secondary
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End point timeframe:

At day 1 after dosing and then every 3 days during the hospitalization

End point values	Tocilizumab	Retrospective cohort at last visit available		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	74	46		
Units: days				
arithmetic mean (standard deviation)				
Time of ICU stay	17.5 (± 16.2)	17.0 (± 16.5)		
Time of ICU stay from the start of tocilizumab	17.8 (± 17.0)	17.0 (± 17.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Organ support therapies

End point title	Organ support therapies
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End point description:

End point type	Secondary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Tocilizumab	Retrospective cohort at last visit available		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	15		
Units: Subjects				
Dialysis	5	3		
Extracorporeal membrane oxygenation	3	2		
Other	12	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Radiological evolution

End point title	Radiological evolution
End point description:	

End point type	Secondary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Tocilizumab	Tocilizumab	Retrospective cohort at screening/visit 1	Retrospective cohort at last visit available
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	438	204	241	124
Units: Subjects				
number (not applicable)				
Normal	3	4	1	3
Abnormal	435	200	240	121

Statistical analyses

No statistical analyses for this end point

Secondary: Serum levels of inflammatory markers: IL-6

End point title	Serum levels of inflammatory markers: IL-6
End point description:	
End point type	Secondary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Tocilizumab	Tocilizumab	Retrospective cohort at screening/visit 1	Retrospective cohort at last visit available
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	62	62	20	20
Units: pg/mL				
arithmetic mean (standard deviation)	142.2 (± 353.6)	523.5 (± 1342.6)	149.4 (± 219.0)	1359.0 (± 2156.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum levels of inflammatory markers: CRP

End point title	Serum levels of inflammatory markers: CRP
End point description:	
End point type	Secondary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Tocilizumab	Tocilizumab	Retrospective cohort at screening/visit 1	Retrospective cohort at last visit available
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	307	307	173	173
Units: mg/L				
arithmetic mean (standard deviation)	106.6 (± 92.0)	13.8 (± 44.4)	114.0 (± 101.0)	18.1 (± 52.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Serum levels of inflammatory markers: D-dimer and Ferritin

End point title	Serum levels of inflammatory markers: D-dimer and Ferritin
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End point description:

End point type	Secondary
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End point timeframe:

At day 1 after dosing and then every 3 days during the hospitalization

End point values	Tocilizumab	Tocilizumab	Retrospective cohort at screening/visit 1	Retrospective cohort at last visit available
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	231 ^[1]	231 ^[2]	130 ^[3]	130 ^[4]
Units: ng/mL				
arithmetic mean (standard deviation)				
D-dimer	1236.0 (± 2141.0)	2072.0 (± 10971.0)	1263.0 (± 2148.0)	2776.0 (± 14532.0)
Ferritin	1401.0 (± 1714.0)	1300.0 (± 4292.0)	1559.0 (± 2159.0)	1073.0 (± 1247.0)

Notes:

[1] - N=231 for D-dimer
N=199 for Ferritin

[2] - N=231 for D-dimer
N=199 for Ferritin

[3] - N=130 for D-dimer
N=108 for Ferritin

[4] - N=130 for D-dimer
N=108 for Ferritin

Statistical analyses

No statistical analyses for this end point

Secondary: Intubation

End point title	Intubation
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End point description:

End point type	Secondary
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End point timeframe:

At day 1 after dosing and then every 3 days during the hospitalization

End point values	Single-dose	Multiple-dose	Retrospective cohort (single dose)	Retrospective cohort (multiple doses)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	337	107	194	53
Units: days				
arithmetic mean (standard deviation)				

Time to intubation	2.2 (± 3.0)	4.3 (± 6.9)	2.1 (± 3.4)	5.6 (± 8.7)
Duration of intubation	16.2 (± 14.5)	20.4 (± 17.1)	15.6 (± 14.4)	19.8 (± 17.0)
Duration of intubation in tocilizumab	16.6 (± 14.5)	24.4 (± 17.4)	15.3 (± 14.3)	24.9 (± 17.7)
Time to NIMV	2.0 (± 4.8)	2.8 (± 5.6)	1.9 (± 6.1)	5.6 (± 7.6)
Duration of NIMV	7.9 (± 8.1)	11.7 (± 8.1)	9.9 (± 10.7)	12.9 (± 9.5)
Duration of NIMV in tocilizumab	8.5 (± 9.3)	12.1 (± 9.4)	9.9 (± 12.3)	13.6 (± 11.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality
End point description:	
End point type	Secondary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Single-dose	Multiple-dose	Retrospective cohort (single dose)	Retrospective cohort (multiple doses)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	337	107	194	53
Units: Subjects				
number (not applicable)				
Yes	65	22	42	14
No	272	85	152	39

Statistical analyses

No statistical analyses for this end point

Secondary: Time to RT-PCR virus negativity

End point title	Time to RT-PCR virus negativity
End point description:	
End point type	Secondary
End point timeframe:	
At day 1 after dosing and then every 3 days during the hospitalization	

End point values	Tocilizumab	Retrospective cohort at screening/visit 1		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	205	127		
Units: days				
median (confidence interval 95%)	27.0 (21.0 to 36.0)	21.0 (16.0 to 30.0)		

Attachments (see zip file)	KM Time to PCR-negativity (overall population).jpg KM Time to PCR-negativity (retrospective population).jpg
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On 1 day after the first dose and every 3 days during the hospitalization

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Overall study
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Reporting group description: -

Serious adverse events	Overall study		
Total subjects affected by serious adverse events			
subjects affected / exposed	145 / 444 (32.66%)		
number of deaths (all causes)	87		
number of deaths resulting from adverse events	85		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypotension			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Shock			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Haemorrhage			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			
subjects affected / exposed	4 / 444 (0.90%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 5		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	75 / 444 (16.89%)		
occurrences causally related to treatment / all	1 / 75		
deaths causally related to treatment / all	1 / 46		
Acute respiratory failure			
subjects affected / exposed	6 / 444 (1.35%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Increased bronchial secretion			

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infiltration			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	4 / 444 (0.90%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pulmonary fibrosis			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Respiratory distress			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	22 / 444 (4.95%)		
occurrences causally related to treatment / all	0 / 22		
deaths causally related to treatment / all	0 / 16		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Red blood cell count decreased			

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	4 / 444 (0.90%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 3		
Myocardial infarction			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ventricular tachycardia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Polyneuropathy			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 444 (0.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Leukocytosis			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	3 / 444 (0.68%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal wall haemorrhage			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Diarrhoea			

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Ileus			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine perforation			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oedematous pancreatitis			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis mesenteric vessel			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cytolysis			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatic ischaemia			

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertransaminaemia			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal impairment			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bacteraemia			
subjects affected / exposed	3 / 444 (0.68%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	2 / 444 (0.45%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	1 / 1		
Bronchopulmonary aspergillosis			

subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cytomegalovirus infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter bacteraemia				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enterococcal bacteraemia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia infection				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Herpes virus infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				

subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia bacterial				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia escherichia				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	2 / 444 (0.45%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Pneumonia pseudomonal				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 444 (0.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Superinfection bacterial				

subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Systemic candida			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tracheobronchitis bacterial			
subjects affected / exposed	1 / 444 (0.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 444 (0.23%)		
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	Overall study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	240 / 444 (54.05%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 444 (1.13%)		
occurrences (all)	5		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	7 / 444 (1.58%)		
occurrences (all)	7		
Cardiac failure			
subjects affected / exposed	5 / 444 (1.13%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Leukocytosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombocytopenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 444 (3.15%)</p> <p>14</p> <p>6 / 444 (1.35%)</p> <p>6</p> <p>11 / 444 (2.48%)</p> <p>11</p>		
<p>Gastrointestinal disorders</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>16 / 444 (3.60%)</p> <p>16</p> <p>8 / 444 (1.80%)</p> <p>8</p> <p>6 / 444 (1.35%)</p> <p>6</p>		
<p>Hepatobiliary disorders</p> <p>Hypertransaminasaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>13 / 444 (2.93%)</p> <p>13</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Acute respiratory failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pulmonary embolism</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Respiratory failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 444 (1.58%)</p> <p>7</p> <p>9 / 444 (2.03%)</p> <p>9</p> <p>24 / 444 (5.41%)</p> <p>24</p>		
<p>Psychiatric disorders</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>6 / 444 (1.35%)</p> <p>6</p>		

Confusional state subjects affected / exposed occurrences (all)	6 / 444 (1.35%) 6		
Insomnia subjects affected / exposed occurrences (all)	20 / 444 (4.50%) 20		
Renal and urinary disorders Acute respiratory distress syndrome subjects affected / exposed occurrences (all)	75 / 444 (16.89%) 75		
Acute kidney injury subjects affected / exposed occurrences (all)	7 / 444 (1.58%) 7		
Infections and infestations Bacteraemia subjects affected / exposed occurrences (all)	5 / 444 (1.13%) 5		
Pneumonia subjects affected / exposed occurrences (all)	5 / 444 (1.13%) 5		
Respiratory tract infection subjects affected / exposed occurrences (all)	6 / 444 (1.35%) 6		
Superinfection bacterial subjects affected / exposed occurrences (all)	5 / 444 (1.13%) 6		
Urinary tract infection subjects affected / exposed occurrences (all)	8 / 444 (1.80%) 8		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	14 / 444 (3.15%) 14		
Hypokalaemia subjects affected / exposed occurrences (all)	6 / 444 (1.35%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2020	Version generated due to clarifications requested by the ethics committee during the initial evaluation of the study
10 February 2021	Change of principal investigator in the following sites: Hospital de la Santa Creu i Sant Pau and Hospital Público General de Tomelloso. HA does not evaluate amendments due to changes in principal investigators.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported