Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia

Summary

EudraCT number	2020-001154-22
Trial protocol	DK DE FR NL GB IT ES
Global end of trial date	28 July 2020

Results information

Result version number	v1 (current)
This version publication date	14 July 2021
First version publication date	14 July 2021

Trial information

Trial identification

Sponsor protocol code	WA42380

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04320615
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	F Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.com
Scientific contact	F Hoffmann-La Roche AG, Hoffmann-La Roche, +41 616878333, global.trial_information@roche.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	22 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in combination with standard of care (SOC) compared with matching placebo in combination with SOC in hospitalized adult participants with severe COVID-19 pneumonia.

Protection of trial subjects:

All participants were required to sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 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	Canada: 15
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	United Kingdom: 65
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	United States: 244
Worldwide total number of subjects	438
EEA total number of subjects	114

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	244
From 65 to 84 years	177
85 years and over	17

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Inclusion Criteria:

- Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- SPO2 </=93% or PaO2/FiO2 <300 mmHg

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Modified Intent-to-Treat (mITT) Arm

Arm description:

Participants randomized to the placebo arm who received any amount of study drug. Participants randomized to the placebo arm were to receive 1 IV infusion of placebo matched to TCZ. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

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

Dosage and administration details:

1 IV infusion of placebo matched to TCZ, with up to 1 additional dose if clinical symptoms worsened or showed no improvement.

Arm title	Tocilizumab (TCZ) mITT Arm

Arm description:

Participants randomized to the TCZ arm who received any amount of study drug. Participants randomized to the TCZ arm were to receive 1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

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

Dosage and administration details:

1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg, with up to 1 additional dose if clinical symptoms worsened or showed no improvement.

Number of subjects in period 1	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm
Started	144	294
Completed	96	190
Not completed	48	104
Consent withdrawn by subject	4	10
Physician decision	2	-
Death	35	71
Unspecified	2	-
Lost to follow-up	5	23

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Modified Intent-to-Treat (mITT) Arm
Reporting group description:	
Participants randomized to the placebo arm who received any amount of study drug. Participants randomized to the placebo arm were to receive 1 IV infusion of placebo matched to TCZ. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.	
Reporting group title	Tocilizumab (TCZ) mITT Arm
Reporting group description:	
Participants randomized to the TCZ arm who received any amount of study drug. Participants randomized to the TCZ arm were to receive 1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.	

Reporting group values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm	Total
Number of subjects	144	294	438
Age categorical Units: Subjects			
Adults (18-64 years)	81	163	244
From 65-84 years	60	117	177
85 years and over	3	14	17
Age Continuous Units: Years			
arithmetic mean	60.6	60.9	
standard deviation	± 13.7	± 14.6	-
Sex: Female, Male Units: Participants			
Female	43	89	132
Male	101	205	306
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	8	13
Asian	10	28	38
Native Hawaiian or Other Pacific Islander	5	3	8
Black or African American	26	40	66
White	76	176	252
More than one race	1	0	1
Unknown or Not Reported	21	39	60
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	47	94	141
Not Hispanic or Latino	86	181	267
Unknown or Not Reported	11	19	30

End points

End points reporting groups

Reporting group title	Placebo Modified Intent-to-Treat (mITT) Arm

Reporting group description:

Participants randomized to the placebo arm who received any amount of study drug. Participants randomized to the placebo arm were to receive 1 IV infusion of placebo matched to TCZ. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

Reporting group title	Tocilizumab (TCZ) mITT Arm

Reporting group description:

Participants randomized to the TCZ arm who received any amount of study drug. Participants randomized to the TCZ arm were to receive 1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

Subject analysis set title	TCZ - No mechanical ventilation at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants randomized to the TCZ arm who received any amount of study drug and were not on mechanical ventilation at baseline. Participants randomized to the TCZ arm were to receive 1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

Subject analysis set title	Placebo - No mechanical ventilation at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants randomized to the placebo arm who received any amount of study drug and were not on mechanical ventilation at baseline. Participants randomized to the placebo arm were to receive 1 IV infusion of placebo matched to TCZ. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

Subject analysis set title	TCZ - Not in ICU at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants randomized to the TCZ arm who received any amount of study drug and were not in the ICU at baseline. Participants randomized to the TCZ arm were to receive 1 intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

Subject analysis set title	Placebo - Not in ICU at baseline
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants randomized to the placebo arm who received any amount of study drug and were not in the ICU at baseline. Participants randomized to the placebo arm were to receive 1 IV infusion of placebo matched to TCZ. Up to 1 additional dose could be given if clinical symptoms worsened or showed no improvement.

Primary: Clinical Status Assessed Using a 7-Category Ordinal Scale at Day 28 (Week 4)

End point title	Clinical Status Assessed Using a 7-Category Ordinal Scale at Day 28 (Week 4)

End point description:

Clinical status was assessed using a 7-category ordinal scale:
1 - Discharged (or "ready for discharge")
2 - Non- intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3 - Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4 - ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5 - ICU, requiring intubation and mechanical ventilation
6 - ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support
7 - Death

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Primary

End point timeframe:

Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Percentage of Participants				
number (not applicable)				
Category 1	49.3	56.5		
Category 2	5.6	2.0		
Category 3	2.8	4.8		
Category 4	6.9	2.0		
Category 5	9.7	8.8		
Category 6	6.3	6.1		
Category 7	19.4	19.7		

Statistical analyses

Statistical analysis title	Clinical Status at Day 28 (Week 4)
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.36
Method	Van Elteren Test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	0

Secondary: Time to Clinical Improvement (TTCI), Defined as a National Early Warning Score 2 (NEWS2) of </= 2 Maintained for 24 Hours

End point title	Time to Clinical Improvement (TTCI), Defined as a National Early Warning Score 2 (NEWS2) of </= 2 Maintained for 24 Hours

End point description:

Defined as time from first dose of study drug to at least two NEWS2 assessments with a score of <=2 covering a span of at least 21.5 hours, with a maximum of 26.5 hours between the first and last of these assessments and no assessments with a score >2 in between. If one of the components of the NEWS2 score was missing at a particular time point, then the NEWS2 score was not calculated. Participants who died were censored at Day 28.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

9999 = Value not estimable (NE) due to an insufficient number of events.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Time to Clinical Improvement
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0443
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.448
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.08

Secondary: Time to Improvement of at Least 2 Categories Relative to Baseline on a 7-Category Ordinal Scale of Clinical Status

End point title	Time to Improvement of at Least 2 Categories Relative to Baseline on a 7-Category Ordinal Scale of Clinical Status

End point description:

Time to improvement for this outcome measure was defined as the days from the first dose of study drug to when at least a 2-category improvement in clinical status (based on a 7-category ordinal scale) is observed. Participants who died were censored at Day 28.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	18.0 (15.0 to 28.0)	14.0 (12.0 to 17.0)		

Statistical analyses

Statistical analysis title	Time to improvement on 7-category scale
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.082
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.263
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.97
upper limit	1.64

Secondary: Time to Hospital Discharge or "Ready for Discharge"

End point title	Time to Hospital Discharge or "Ready for Discharge"

End point description:

Time to Hospital Discharge was defined as the time from the first dose of study drug to hospital discharge or "ready for discharge" (normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or </=2L supplemental oxygen). Participants who died were censored at Day 28.

9999 = Value not estimable (NE) due to an insufficient number of events.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	28.0 (20.0 to 9999)	20.0 (17.0 to 27.0)		

Statistical analyses

Statistical analysis title	Time to hospital discharge or ready for discharge
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.037
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.79

Secondary: Incidence of Mechanical Ventilation by Day 28

End point title	Incidence of Mechanical Ventilation by Day 28

End point description:

Participants who died by Day 28 were assumed to have required mechanical ventilation.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm	TCZ - No mechanical ventilation at baseline	Placebo - No mechanical ventilation at baseline
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	144	294	183	90
Units: Percentage of Participants				
number (confidence interval 95%)	60.4 (52.4 to 68.4)	54.4 (48.7 to 60.1)	27.9 (21.4 to 34.4)	36.7 (26.7 to 46.6)

Statistical analyses

Statistical analysis title	Incidence of mechanical ventilation by Day 28
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0996
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-6.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	1.4

Statistical analysis title	Incidence of mechanical ventilation by Day 28
Comparison groups	TCZ - No mechanical ventilation at baseline v Placebo - No mechanical ventilation at baseline
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1355
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-8.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.7
upper limit	3

Secondary: Ventilator-Free Days to Day 28

End point title	Ventilator-Free Days to Day 28

End point description:

Participants who died by Day 28 were assigned 0 ventilator-free days.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	16.5 (11.0 to 26.0)	22.0 (18.0 to 28.0)		

Statistical analyses

Statistical analysis title	Ventilator-free days to Day 28
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3202
Method	Van Elteren test
Parameter estimate	Median difference (final values)
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	13

Secondary: Incidence of Intensive Care Unit (ICU) Stay by Day 28 (Week 4)

End point title	Incidence of Intensive Care Unit (ICU) Stay by Day 28 (Week 4)

End point description:

Participants who died by Day 28 were assumed to have required an ICU stay.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm	TCZ - Not in ICU at baseline	Placebo - Not in ICU at baseline
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	144	294	127	64
Units: Percentage of Participants				
number (confidence interval 95%)	71.5 (64.2 to 78.9)	66.0 (60.6 to 71.4)	21.3 (14.1 to 28.4)	35.9 (24.2 to 47.7)

Statistical analyses

Statistical analysis title	Incidence of ICU stay by Day 28
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1514
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	2.2

Statistical analysis title	Incidence of ICU stay by Day 28
Comparison groups	TCZ - Not in ICU at baseline v Placebo - Not in ICU at baseline
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.029
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-14.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.6
upper limit	-1

Secondary: Duration of ICU Stay to Day 28 (Week 4)

End point title	Duration of ICU Stay to Day 28 (Week 4)

End point description:

Participants who died by Day 28 were assigned a duration from the first dose of study drug to Day 28 at hour 23:59:59.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	15.5 (8.7 to 25.5)	9.8 (7.0 to 15.7)		

Statistical analyses

Statistical analysis title	Duration of ICU stay to Day 28
Comparison groups	Tocilizumab (TCZ) mITT Arm v Placebo Modified Intent-to-Treat (mITT) Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0454
Method	Van Elteren test
Parameter estimate	Median difference (final values)
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15
upper limit	2.9

Secondary: Clinical Status Assessed Using a 7-Category Ordinal Scale at Day 14

End point title	Clinical Status Assessed Using a 7-Category Ordinal Scale at Day 14

End point description:

Clinical status was assessed using a 7-category ordinal scale:
1 - Discharged (or "ready for discharge")
2 - Non- intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3 - Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen
4 - ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5 - ICU, requiring intubation and mechanical ventilation
6 - ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support
7 - Death

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Day 14

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Percentage of Participants				
number (not applicable)				
Category 1	29.9	39.8		
Category 2	4.9	6.1		
Category 3	11.1	6.5		
Category 4	7.6	7.1		
Category 5	16.0	14.6		
Category 6	17.4	12.6		
Category 7	13.2	13.3		

Statistical analyses

Statistical analysis title	Clinical status on 7-category scale at Day 14
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm

Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0548
Method	Van Elteren test
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	0.5

Secondary: Time to Clinical Failure to Day 28 (Week 4)

End point title	Time to Clinical Failure to Day 28 (Week 4)

End point description:

Time to clinical failure was defined as the number of days from the first dose of study drug to the first occurrence on study of death, mechanical ventilation, ICU admission, or study withdrawal prior to discharge, whichever occurs first.

9999 = Value not estimable (NE) due to an insufficient number of events.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	9999 (21.0 to 9999)	9999 (9999 to 9999)		

Statistical analyses

Statistical analysis title	Time to clinical failure to Day 28
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm

Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1627
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.1

Secondary: Mortality Rate at Day 28 (week 4)

End point title	Mortality Rate at Day 28 (week 4)

End point description:

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Percentage of Participants				
number (confidence interval 95%)	19.4 (13.0 to 25.9)	19.7 (15.2 to 24.3)		

Statistical analyses

Statistical analysis title	Mortality rate at Day 28
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.941
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	8.2

Secondary: Time to Recovery to Day 28 (Week 4)

End point title	Time to Recovery to Day 28 (Week 4)

End point description:

Time to recovery was defined as the number of days from the first dose of study drug to hospital discharge or "ready for discharge" (normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or </= 2L supplemental oxygen) or non-ICU hospital ward or "ready for hospital ward" not requiring supplemental oxygen. Participants who died were censored at Day 28.

9999 = Value not estimable (NE) due to an insufficient number of events.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	24.0 (18.0 to 9999)	16.0 (12.0 to 21.0)		

Statistical analyses

Statistical analysis title	Time to recovery to Day 28
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0528
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.307

Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.72

Secondary: Duration of Supplemental Oxygen to Day 28 (Week 4)

End point title	Duration of Supplemental Oxygen to Day 28 (Week 4)

End point description:

Participants who died by Day 28 were assigned a duration of 28 days of supplemental oxygen.

mITT population: Defined as all randomized participants who received any amount of study medication, with participants grouped according to the treatment assigned at randomization.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Placebo Modified Intent-to-Treat (mITT) Arm	Tocilizumab (TCZ) mITT Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	294		
Units: Days				
median (confidence interval 95%)	28.0 (26.0 to 28.0)	26.5 (19.0 to 28.0)		

Statistical analyses

Statistical analysis title	Duration of supplemental oxygen to Day 28
Comparison groups	Placebo Modified Intent-to-Treat (mITT) Arm v Tocilizumab (TCZ) mITT Arm
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0477
Method	Van Elteren test
Parameter estimate	Median difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9
upper limit	0.5

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
60 days	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Placebo Arm (Safety-Evaluable Population)
Reporting group description:	
All participants who received any amount of study medication. Participants are grouped according to the treatment first received rather than the treatment assigned at randomization.	
Reporting group title	Tocilizumab (TCZ) Arm (Safety-Evaluable Population)
Reporting group description:	
All participants who received any amount of study medication. Participants are grouped according to the treatment first received rather than the treatment assigned at randomization.	

Serious adverse events	Placebo Arm (Safety-Evaluable Population)	Tocilizumab (TCZ) Arm (Safety-Evaluable Population)	
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 143 (44.76%)	116 / 295 (39.32%)	
number of deaths (all causes)	36	72	
number of deaths resulting from adverse events			
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertension			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 143 (0.70%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 143 (0.70%)	5 / 295 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	1 / 5	
Pyrexia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	2 / 143 (1.40%)	4 / 295 (1.36%)		
occurrences causally related to treatment / all	0 / 2	0 / 4		
deaths causally related to treatment / all	0 / 2	0 / 2		
Acute respiratory failure				
subjects affected / exposed	2 / 143 (1.40%)	2 / 295 (0.68%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 2	0 / 1		
Aspiration				
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Haemothorax				
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hypoxia				
subjects affected / exposed	3 / 143 (2.10%)	0 / 295 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lung consolidation				
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Obstructive airways disorder				
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pharyngeal haemorrhage				
subjects affected / exposed	2 / 143 (1.40%)	0 / 295 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Pneumonia aspiration				

subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 143 (2.10%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 143 (1.40%)	5 / 295 (1.69%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory disorder			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 143 (4.20%)	5 / 295 (1.69%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 3	0 / 3	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 143 (0.70%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Citrobacter test positive			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcus test positive			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related acute lung injury			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina unstable			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 143 (0.00%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	5 / 143 (3.50%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 143 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	2 / 143 (1.40%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Seizure			
subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eosinophilia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 143 (0.00%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia perforation			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 143 (0.70%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Small intestinal obstruction			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 143 (2.80%)	10 / 295 (3.39%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure			
subjects affected / exposed	2 / 143 (1.40%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	3 / 143 (2.10%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacterial sepsis			
subjects affected / exposed	0 / 143 (0.00%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 143 (1.40%)	14 / 295 (4.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 14	
deaths causally related to treatment / all	0 / 2	0 / 13	
COVID-19 pneumonia			
subjects affected / exposed	20 / 143 (13.99%)	36 / 295 (12.20%)	
occurrences causally related to treatment / all	0 / 20	0 / 36	
deaths causally related to treatment / all	0 / 20	0 / 36	
Candida infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus hepatitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter pneumonia			

subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 143 (2.80%)	7 / 295 (2.37%)	
occurrences causally related to treatment / all	3 / 5	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 143 (1.40%)	6 / 295 (2.03%)	
occurrences causally related to treatment / all	1 / 2	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 143 (2.80%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	1 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	7 / 143 (4.90%)	7 / 295 (2.37%)	
occurrences causally related to treatment / all	3 / 8	3 / 7	
deaths causally related to treatment / all	0 / 1	1 / 2	
Staphylococcal infection			
subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stenotrophomonas infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis bacterial			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	0 / 143 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 143 (0.70%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 143 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	1 / 143 (0.70%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo Arm (Safety-Evaluable Population)	Tocilizumab (TCZ) Arm (Safety-Evaluable Population)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 143 (20.28%)	83 / 295 (28.14%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 143 (2.10%)	20 / 295 (6.78%)	
occurrences (all)	4	24	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 143 (6.99%)	17 / 295 (5.76%)	
occurrences (all)	10	17	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 143 (5.59%)	18 / 295 (6.10%)	
occurrences (all)	8	18	
Diarrhoea			
subjects affected / exposed	3 / 143 (2.10%)	18 / 295 (6.10%)	
occurrences (all)	3	18	
Infections and infestations			
Pneumonia			
subjects affected / exposed	8 / 143 (5.59%)	10 / 295 (3.39%)	
occurrences (all)	12	10	
Urinary tract infection			
subjects affected / exposed	5 / 143 (3.50%)	22 / 295 (7.46%)	
occurrences (all)	6	22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 April 2020	Removed secondary efficacy objective; updated eligibility criteria; updated text for time to clinical failure outcome measure; clarification text for ordinal scale interpretation.
11 June 2020	Added secondary efficacy endpoint; defined key secondary endpoints.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported