Clinical trial results:
An Adaptive Phase 3, Randomized, Double-blind, Placebo-controlled, Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients With COVID-19

Summary

EudraCT number	2020-001162-12
Trial protocol	DE FR IT ES
Global end of trial date	02 September 2020

Results information

Result version number	v1
This version publication date	02 June 2021
First version publication date	02 June 2021

Trial information

Trial identification

Sponsor protocol code	EFC16844

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04327388
WHO universal trial number (UTN)	U1111-1249-6021

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly Mazarin Cedex, France, 91385
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	28 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of sarilumab relative to the control arm in adult subjects hospitalised with severe or critical Coronavirus Disease 2019 (COVID-19).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 43
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Brazil: 77
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Chile: 59
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Russian Federation: 113
Worldwide total number of subjects	420
EEA total number of subjects	123

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)	290
From 65 to 84 years	114
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 46 active centres in 11 countries. 431 subjects were screened between 28 March 2020 and 02 July 2020, of which 10 had screen failures due to exclusion criteria met. 420 subjects were randomised in treatment by interactive response technology (IRT) (2:2:1 ratio) to receive sarilumab 200 milligrams (mg)/400mg and placebo.

Pre-assignment

Screening details:

Randomisation was stratified by severity of illness (severe disease, critical disease) and use of systemic corticosteroids (Yes/No). One subject was randomised twice and thus excluded from randomisation.

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	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Sarilumab 200 mg

Arm description:

Sarilumab 200 mg, single dose of intravenous (IV) injection on Day 1. Subjects could receive a second dose of sarilumab 200 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
• Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
• Increase/recurrence of fever or
• Increase/no change in fraction of inspired oxygen (FiO2) requirement or
• Required vasopressors, extracorporeal membrane oxygenation (ECMO) or development of multi-organ dysfunction.

Arm type	Experimental
Investigational medicinal product name	Sarilumab
Investigational medicinal product code	SAR153191
Other name	Kevzara®
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

200 mg, single dose of IV injection on Day 1.

Arm title	Sarilumab 400 mg

Arm description:

Sarilumab 400 mg, single dose of IV injection on Day 1. Subjects could receive a second dose of sarilumab 400 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Arm type	Experimental

Investigational medicinal product name	Sarilumab
Investigational medicinal product code	SAR153191
Other name	Kevzara®
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

400 mg, single dose of IV injection on Day 1.

Arm title	Placebo

Arm description:

Placebo (for sarilumab), single dose of IV injection on Day 1. Subjects could receive a second dose of placebo (for sarilumab) 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

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

Dosage and administration details:

Placebo matching sarilumab, single dose of IV injection on Day 1.

Number of subjects in period 1	Sarilumab 200 mg	Sarilumab 400 mg	Placebo
Started	161	173	86
Treated	159	173	84
Subjects Who Received Second Dose	13 [1]	11 [2]	5 [3]
Completed	141	153	75
Not completed	20	20	11
Randomised and not treated	2	-	2
Adverse Event	17	18	9
Unspecified	1	2	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects who met prespecified criteria as per protocol amendment 2, received a second dose of the study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects who met prespecified criteria as per protocol amendment 2, received a second dose of the study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Subjects who met prespecified criteria as per protocol amendment 2, received a second dose of the study drug (based on the original treatment group assigned) 24 to 48 hours after the first dose.

Baseline characteristics

Reporting groups	
Reporting group title	Sarilumab 200 mg

Reporting group description:

Sarilumab 200 mg, single dose of intravenous (IV) injection on Day 1. Subjects could receive a second dose of sarilumab 200 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
• Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
• Increase/recurrence of fever or
• Increase/no change in fraction of inspired oxygen (FiO2) requirement or
• Required vasopressors, extracorporeal membrane oxygenation (ECMO) or development of multi-organ dysfunction.

Reporting group title	Sarilumab 400 mg

Reporting group description:

Sarilumab 400 mg, single dose of IV injection on Day 1. Subjects could receive a second dose of sarilumab 400 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Reporting group title	Placebo

Reporting group description:

Placebo (for sarilumab), single dose of IV injection on Day 1. Subjects could receive a second dose of placebo (for sarilumab) 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Reporting group values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo
Number of subjects	161	173	86
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.3	58.0	59.9
standard deviation	± 13.7	± 14.1	± 14.8
Gender categorical Units: Subjects			
Female	52	74	30
Male	109	99	56
Race Units: Subjects			
American Indian or Alaska Native	2	2	1
Asian	5	9	6
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	3	5	1

White	128	128	69
More than one race	0	3	0
Not Reported	23	26	8
Clinical Status: 7-point ordinal scale			
7-point ordinal scale with scores range from: 1= death; 2= hospitalised, on invasive mechanical ventilation or ECMO; 3= hospitalised, on non-invasive ventilation/high flow oxygen devices; 4= hospitalised, requiring supplemental oxygen; 5= hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related/otherwise); 6= hospitalised, not requiring supplemental oxygen - no longer required ongoing medical care; 7= not hospitalised, higher score = less severity. Number of subjects in each scale category were reported.			
Units: Subjects			
Scale Score 1	0	0	0
Scale Score 2	17	24	10
Scale Score 3	28	21	11
Scale Score 4	113	128	65
Scale Score 5	3	0	0
Scale Score 6	0	0	0
Scale Score 7	0	0	0

Reporting group values	Total		
Number of subjects	420		
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	156		
Male	264		
Race			
Units: Subjects			
American Indian or Alaska Native	5		
Asian	20		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	9		
White	325		
More than one race	3		
Not Reported	57		
Clinical Status: 7-point ordinal scale			
7-point ordinal scale with scores range from: 1= death; 2= hospitalised, on invasive mechanical ventilation or ECMO; 3= hospitalised, on non-invasive ventilation/high flow oxygen devices; 4= hospitalised, requiring supplemental oxygen; 5= hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related/otherwise); 6= hospitalised, not requiring supplemental oxygen - no longer required ongoing medical care; 7= not hospitalised, higher score = less severity. Number of subjects in each scale category were reported.			
Units: Subjects			
Scale Score 1	0		
Scale Score 2	51		
Scale Score 3	60		
Scale Score 4	306		

Scale Score 5	3		
Scale Score 6	0		
Scale Score 7	0		

End points

End points reporting groups

Reporting group title	Sarilumab 200 mg

Reporting group description:

Sarilumab 200 mg, single dose of intravenous (IV) injection on Day 1. Subjects could receive a second dose of sarilumab 200 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
• Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
• Increase/recurrence of fever or
• Increase/no change in fraction of inspired oxygen (FiO2) requirement or
• Required vasopressors, extracorporeal membrane oxygenation (ECMO) or development of multi-organ dysfunction.

Reporting group title	Sarilumab 400 mg

Reporting group description:

Sarilumab 400 mg, single dose of IV injection on Day 1. Subjects could receive a second dose of sarilumab 400 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Reporting group title	Placebo

Reporting group description:

Placebo (for sarilumab), single dose of IV injection on Day 1. Subjects could receive a second dose of placebo (for sarilumab) 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Primary: Time to Improvement in Clinical Status of Subjects (Using 7-point Ordinal Scale Score) by at Least 2 Points

End point title	Time to Improvement in Clinical Status of Subjects (Using 7-point Ordinal Scale Score) by at Least 2 Points

End point description:

Time to improvement of greater than or equal to (>=) 2 points in clinical status (CS) assessment-defined as time (in days) from 1st dose of study drug to time of 1st occurrence of improvement of >=2 points in CS of subjects assessed using 7-point ordinal scale (calculated as:date of first occurrence/episode of event – date of first dose + 1). Seven-point ordinal scale for clinical assessment ranges from 1=death; 2=hospitalised (H), on invasive mechanical ventilation/ECMO; 3=H, on non-invasive ventilation/high flow oxygen devices; 4=H, requiring supplemental oxygen; 5=H, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related/otherwise); 6=H, not requiring supplemental oxygen - no longer required ongoing medical care; 7=not H, higher score = less severity. Kaplan-Meier method was used for analysis. Modified intention-to-treat (mITT) population-treated with study medication and were analysed according to initial treatment assigned to subject (as randomised).

End point type	Primary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: days				
median (confidence interval 95%)	10.0 (9.00 to 12.00)	10.0 (9.00 to 13.00)	12.0 (9.00 to 15.00)	

Statistical analyses

Statistical analysis title	Sarilumab 200 mg versus Placebo

Statistical analysis description:

Hazard ratio for estimation of treatment effect of each sarilumab dose versus placebo was assessed by cox proportional hazard model stratified by severity of illness (severe, critical) and use of systemic corticosteroids (Yes, No) as entered in IRT.

Comparison groups	Sarilumab 200 mg v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9561 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.751
upper limit	1.402

Notes:

[1] - Analysed based on log-rank test stratified by severity of illness (severe, critical) and use of systemic corticosteroids (Yes, No) as entered in IRT.

Statistical analysis title	Sarilumab 400 mg versus Placebo

Statistical analysis description:

Hazard ratio for estimation of treatment effect of each sarilumab dose versus placebo was assessed by cox proportional hazard model stratified by severity of illness (severe, critical) and use of systemic corticosteroids (Yes, No) as entered in IRT.

Comparison groups	Sarilumab 400 mg v Placebo
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3376 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.135
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.835
upper limit	1.543

Notes:

[2] - Analysed based on logrank test stratified by severity of illness (severe, critical) and use of systemic corticosteroids (Yes, No) as entered in IRT.

Secondary: Percentage of Subjects Who Were Alive at Day 29

End point title	Percentage of Subjects Who Were Alive at Day 29

End point description:

Percentage of subjects who were alive at Day 29 were reported in this endpoint. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: percentage of subjects				
number (not applicable)	89.9	91.9	91.7	

Statistical analyses

Statistical analysis title	Sarilumab 200 mg versus Placebo
Comparison groups	Placebo v Sarilumab 200 mg
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.628 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.27
upper limit	5.81

Notes:

[3] - By Cochran-Mantel-Haenszel test stratified by severity of illness (severe, critical) and use of systemic corticosteroids (Yes, No) as entered in IRT.

Statistical analysis title	Sarilumab 400 mg versus Placebo
Comparison groups	Sarilumab 400 mg v Placebo

Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8478 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in percentage
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.93
upper limit	7.41

Notes:

[4] - By Cochran-Mantel-Haenszel test stratified by severity of illness (severe, critical) and use of systemic corticosteroids (Yes, No) as entered in IRT.

Secondary: Percentage of Subjects With Improvement in Clinical Status (According to 7-point Ordinal Scale Score) by at Least 1 Point From Baseline at Days 4, 7, 15, 21, and 29

End point title	Percentage of Subjects With Improvement in Clinical Status (According to 7-point Ordinal Scale Score) by at Least 1 Point From Baseline at Days 4, 7, 15, 21, and 29

End point description:

Clinical status of subjects was assessed using 7-point ordinal scale ranges from: 1=death; 2=hospitalised, on invasive mechanical ventilation/ECMO; 3=hospitalised, on non-invasive ventilation/high flow oxygen devices; 4=hospitalised, requiring supplemental oxygen; 5=hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related/otherwise); 6=hospitalised, not requiring supplemental oxygen - no longer required ongoing medical care; 7=not hospitalised, higher score=less severity. Percentage of subjects with >=1 point improvement in clinical status from Baseline at Days 4, 7, 15, 21, and 29 (assessed using the 7-point ordinal scale) were reported. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline, Days 4, 7, 15, 21, and 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: percentage of subjects				
number (not applicable)				
Day 4	25.2	25.4	23.8	
Day 7	51.6	48.6	42.9	
Day 15	74.8	76.9	71.4	
Day 21	80.5	81.5	85.7	
Day 29	84.9	84.4	88.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Days 4, 7, 15, 21, 29 in 7-point Ordinal Scale Score

End point title	Change From Baseline at Days 4, 7, 15, 21, 29 in 7-point Ordinal Scale Score

End point description:

Clinical status of subjects was assessed using 7-point ordinal scale ranges from: 1=death; 2=hospitalised, on invasive mechanical ventilation/ECMO; 3=hospitalised, on non-invasive ventilation/high flow oxygen devices; 4=hospitalised, requiring supplemental oxygen; 5=hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related/otherwise); 6=hospitalised, not requiring supplemental oxygen - no longer required ongoing medical care; 7=not hospitalised, higher score=less severity. Analysis was performed on mITT population. Here, 'n' = subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Days 4, 7, 15, 21, and 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: scores on a scale				
arithmetic mean (standard deviation)				
Day 4 (n = 159, 173, 84)	0.1 (± 0.9)	0.1 (± 1.0)	0.2 (± 0.9)	
Day 7 (n = 159, 173, 84)	0.7 (± 1.5)	0.7 (± 1.6)	0.7 (± 1.4)	
Day 15 (n = 158, 171, 83)	1.9 (± 1.8)	2.0 (± 1.9)	1.7 (± 1.8)	
Day 21 (n = 155, 169, 83)	2.3 (± 1.9)	2.3 (± 1.9)	2.5 (± 1.7)	
Day 29 (n = 156, 170, 83)	2.5 (± 1.9)	2.5 (± 1.9)	2.7 (± 1.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Fever

End point title	Time to Resolution of Fever

End point description:

Resolution of fever was defined as body temperature less than or equal to (<=) 36.6 degree Celsius (°C) (axilla), or <=37.2°C (oral), or <=37.8°C (rectal or tympanic) for at least 48 hours without antipyretics/until discharge, whichever was sooner. Time to resolution of fever (in days) was calculated as: date of first ccurrence/episode of the event (resolution of fever) - date of first dose + 1. Kaplan-Meier method was used for estimation. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: days				
median (confidence interval 95%)	8.0 (7.00 to 9.00)	9.0 (7.00 to 10.00)	7.00 (6.00 to 12.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Fever and Improvement in Oxygenation

End point title	Time to Resolution of Fever and Improvement in Oxygenation

End point description:

Time to resolution of fever was defined as body temperature <=36.6°C (axilla), or <=37.2 °C (oral), or <=37.8°C (rectal or tympanic) for at least 48 hours without antipyretics or until discharge, whichever was sooner. Improvement in oxygenation was defined as oxygen saturation (SpO2)/FiO2 of 50 or greater compared to the nadir SpO2/FiO2 for at least 48 hours, or until discharge, whichever was sooner. Nadir SpO2/FiO2 was the nadir (lowest value) at any point in the study. Time to resolution of fever and improvement in oxygenation (in days) was calculated as: date of first occurrence/episode of the event (resolution of fever and improvement in oxygenation) - date of first dose + 1. Kaplan-Meier method was used for estimation. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: days				
median (confidence interval 95%)	9.0 (8.00 to 10.00)	10.0 (9.00 to 13.00)	8.0 (7.00 to 12.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days With Fever

End point title	Number of Days With Fever

End point description:

Fever was defined as body temperature greater than (>) 37.4°C (axilla), or >38.0 °C (oral), or >38.4°C (rectal or tympanic) based on maximum value observed during a 24-hour period. Number of days with fever were reported. Least square (LS) mean and standard error (SE) were estimated using the analysis of covariance (ANCOVA) model with treatment group and randomisation strata as fixed effects. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary
End point timeframe: Baseline to Day 29	

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	143	159	77	
Units: days				
least squares mean (standard error)	1.2 (± 0.23)	1.3 (± 0.21)	1.8 (± 0.30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects in Each National Early Warning Score 2 (NEWS2) Clinical Risk Category at Baseline and at Days 4, 7, 15, 21, and 29

End point title	Percentage of Subjects in Each National Early Warning Score 2 (NEWS2) Clinical Risk Category at Baseline and at Days 4, 7, 15, 21, and 29

End point description:

NEWS2:standardises assessment of acute-illness severity,track clinical condition & alert clinical teams to subject deterioration. NEWS2 score:based on 7 clinical parameters:respiration rate, oxygen (O2) saturation,supplemental O2,systolic blood pressure, pulse rate,level of consciousness & temperature. Score of 0,1,2 & 3 was allocated to each parameter except supplemental O2(score of 0 or 1) & level of consciousness (score of 0 or 3), where 0=normal health condition to 3=worst health condition;higher score=more severity. All scores were summed to get an aggregate score which ranged from 0 to 19, higher scores=more severity/higher risk. Percentage of subjects in following clinical risk categories were reported:low risk(score 0 - 4);low to medium risk(score of 3 in any individual parameter);medium risk (score 5 - 6);high risk (score 7 - 19). mITT population. 'Number of subjects analysed'=subjects evaluable for this endpoint & 'n'=subjects with available data for each specified category.

End point type	Secondary
End point timeframe: Baseline, Days 4, 7, 15, 21, and 29	

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	169	84	
Units: percentage of subjects				
number (not applicable)				
Baseline: Low (n = 146, 163, 79)	28.8	22.1	34.2	
Baseline: Low to Medium (n = 146, 163, 79)	0	0	0	
Baseline: Medium (n = 146, 163, 79)	34.2	37.4	27.8	
Baseline: High (n = 146, 163, 79)	37.0	40.5	38.0	
Day 4: Low (n = 159, 169, 84)	52.8	56.2	40.5	

Day 4: Low to Meium (n = 159, 169, 84)	0.6	1.2	0	
Day 4: Medium (n = 159, 169, 84)	19.5	16.6	28.6	
Day 4: High (n = 159, 169, 84)	27.0	26.0	31.0	
Day 7: Low (n = 135, 143, 74)	57.0	60.8	51.4	
Day 7: Low to Medium (n = 135, 143, 74)	0	2.1	0	
Day 7: Medium (n = 135, 143, 74)	20.0	10.5	20.3	
Day 7: High (n = 135, 143, 74)	23.0	26.6	28.4	
Day 15: Low (n = 61, 67, 36)	52.5	52.2	61.1	
Day 15: Low to Medium (n = 61, 67, 36)	0	1.5	2.8	
Day 15: Medium (n = 61, 67, 36)	21.3	19.4	13.9	
Day 15: High (n = 61, 67, 36)	26.2	26.9	22.2	
Day 21: Low (n = 29, 38, 12)	44.8	50.0	66.7	
Day 21: Low to Medium (n = 29, 38, 12)	13.8	0	0	
Day 21: Medium (n = 29, 38, 12)	24.1	21.1	8.3	
Day 21: High (n = 29, 38, 12)	17.2	28.9	25.0	
Day 29: Low (n = 14, 18, 5)	57.1	27.8	60.0	
Day 29: Low to Medium (n = 14, 18, 5)	0	0	0	
Day 29: Medium (n = 14, 18, 5)	14.3	27.8	20.0	
Day 29: High (n = 14, 18, 5)	28.6	44.4	20.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to National Early Warning Score of Less Than (<) 2 and Maintained for 24 Hours

End point title	Time to National Early Warning Score of Less Than (<) 2 and Maintained for 24 Hours

End point description:

Time to NEWS2 <2 and maintained for 24 hours :time (in days) from 1st dose of study drug until 1st occurrence of NEWS score of <2 (maintained for 24 hours); calculated as: date of 1st occurrence/episode of event (NEWS score of <2) – date of first dose + 1. NEWS2 score was based on 7 clinical parameters: respiration rate, oxygen saturation, supplemental oxygen, systolic blood pressure, pulse rate, level of consciousness, and temperature. A score of 0, 1, 2 and 3 was allocated to each parameter except supplemental oxygen (score of 0 or 1 was allocated) and level of consciousness (score of 0 or 3 was allocated), where 0=normal health condition to 3=worst health condition; higher score=more severity. All scores were summed to get an aggregate score which ranged from 0 to 19, with higher scores=more severity/higher risk. Kaplan-Meier method was used for analysis. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: days				
median (confidence interval 95%)	9.0 (7.00 to 10.00)	9.0 (8.00 to 11.00)	11.0 (8.00 to 14.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline at Days 4, 7, 15, 21, and 29 in National Early Warning Score 2

End point title	Change From Baseline at Days 4, 7, 15, 21, and 29 in National Early Warning Score 2

End point description:

NEWS2:standardises assessment of acute-illness severity,track clinical condition & alert clinical teams to subject deterioration. NEWS2 score:based on 7 clinical parameters:respiration rate, oxygen (O2) saturation,supplemental O2,systolic blood pressure, pulse rate,level of consciousness & temperature. Score of 0,1,2 & 3 was allocated to each parameter except supplemental O2(score of 0 or 1) & level of consciousness(score of 0 or 3), where 0=normal health condition to 3=worst health condition;higher score=more severity. All scores were summed to get an aggregate score which ranged from 0 to 19, higher scores=more severity/higher risk. Percentage of subjects in following clinical risk categories were reported: low risk(score 0 - 4);low to medium risk(score of 3 in any individual parameter);medium risk (score 5 - 6);high risk (score 7 - 19). mITT population. 'Number of subjects analysed'=subjects evaluable for this endpoint & 'n'=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline, Days 4, 7, 15, 21, and 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	146	159	79	
Units: scores on a scale				
least squares mean (standard error)				
Day 4 (n = 146, 159, 79)	-1.07 (± 0.212)	-1.25 (± 0.198)	-0.36 (± 0.274)	
Day 7 (n = 122, 133, 69)	-1.63 (± 0.265)	-1.47 (± 0.245)	-0.83 (± 0.338)	
Day 15 (n = 55, 62, 33)	-2.10 (± 0.508)	-1.83 (± 0.467)	-2.36 (± 0.641)	
Day 21 (n = 26, 34, 12)	-3.02 (± 0.769)	-2.24 (± 0.676)	-2.96 (± 1.090)	
Day 29 (n = 13, 17, 5)	-2.57 (± 0.936)	-1.27 (± 0.884)	-3.64 (± 1.508)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-improvement in Oxygenation

End point title	Time-to-improvement in Oxygenation

End point description:

Time-to-improvement in oxygenation was defined as increase in SpO2/FiO2 of 50 or greater compared to the nadir SpO2/FiO2 for at least 48 hours or until discharge, whichever was sooner. Nadir SpO2/FiO2 was the nadir (lowest value) at any point in the study. Time to improvement in oxygenation was calculated as: date of first occurrence/episode of the event (oxygenation) – date of first dose + 1. Kaplan-Meier method was used for estimation. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: days				
median (confidence interval 95%)	6.0 (5.00 to 7.00)	6.0 (5.00 to 7.00)	7.0 (5.00 to 8.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Alive Off Supplemental Oxygen at Day 29

End point title	Percentage of Subjects Alive Off Supplemental Oxygen at Day 29

End point description:

Supplemental oxygen was defined as oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: percentage of subjects				
number (not applicable)	84.9	83.8	86.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days With Hypoxemia

End point title	Percentage of Days With Hypoxemia

End point description:

Hypoxemia (low level of oxygen in the blood) was defined as SpO2 <93% on room air, or required supplemental oxygen, or mechanical ventilatory support. Days meeting the criteria for hypoxemia since the first study dose were counted and the percentage of days with hypoxemia were calculated as: 100*number of days with the hypoxemia divided by number of days of follow up (defined as the earlier date of death or discharge or last visit up to Day 29). LS mean and SE were estimated using the ANCOVA model with treatment group and randomisation strata as fixed effects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: percentage of days				
least squares mean (standard error)	73.01 (± 2.063)	75.10 (± 1.941)	76.32 (± 2.724)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days With Supplemental Oxygen Use

End point title	Percentage of Days With Supplemental Oxygen Use

End point description:

Supplemental oxygen (oxygen therapy) was defined as oxygen administration using oxygen delivery device (e.g. nasal cannula, simple face mask, non-rebreather mask, high flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, extracorporeal life support, etc.). Days meeting the criteria for supplemental oxygen use since the first study dose were counted and the percentage of days with supplemental oxygen use were calculated as: 100*number of days with the supplemental oxygen use divided by number of days of follow up (defined as the earlier date of death or discharge or last visit up to Day 29). LS mean and SE were estimated using the ANCOVA model with treatment group and randomisation strata as fixed effects. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: percentage of days				
least squares mean (standard error)	70.57 (± 2.082)	73.30 (± 1.959)	73.23 (± 2.748)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days With Resting Respiratory Rate >24 Breaths Per Minute

End point title	Percentage of Days With Resting Respiratory Rate >24 Breaths Per Minute

End point description:

Resting respiratory rate was measured in terms of number of breaths per minute (bpm) while a person is at rest. Only the days with respiratory rate >24 breath per minute since the first dose were counted and percentage of days with respiratory rate >24 bpm were calculated as: 100*number of days with respiratory rate >24 bpm divided by number of days of follow up (defined as the earlier date of death or discharge or last visit up to Day 29). LS mean and SE were estimated using the ANCOVA model with treatment group and randomisation strata as fixed effects. Analysis was performed on mITT population. Here,'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	150	164	78	
Units: percentage of days				
least squares mean (standard error)	14.74 (± 1.582)	14.58 (± 1.485)	15.74 (± 2.105)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Oxygen Saturation >=94% on Room Air

End point title	Time to Oxygen Saturation >=94% on Room Air

End point description:

Time to oxygen saturation >=94% on room air was defined as the time (in days) from first dose of study drug until the time of first occurrence of oxygen saturation >=94% and it was calculated as: date of first occurrence/episode of the event (oxygen saturation >=94%) – date of first dose + 1. Kaplan-Meier method was used for estimation. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: days				
median (confidence interval 95%)	8.0 (6.00 to 10.00)	8.0 (8.00 to 11.00)	8.0 (7.00 to 11.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Ventilator Free Days

End point title	Mean Number of Ventilator Free Days

End point description:

Mean number of ventilator free days in subjects were reported. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: days				
arithmetic mean (standard deviation)	23.8 (± 9.4)	24.0 (± 8.8)	24.9 (± 8.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Initiation of Mechanical Ventilation, Non-invasive Ventilation, or Use of High Flow Nasal Cannula

End point title	Percentage of Subjects With Initiation of Mechanical Ventilation, Non-invasive Ventilation, or Use of High Flow Nasal Cannula

End point description:

Percentage of subjects with initiation of mechanical ventilation or non-invasive ventilation or use of high flow nasal cannula were reported in this endpoint. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	127	141	68	
Units: percentage of subjects				
number (not applicable)	20.5	23.4	19.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Required Rescue Medication

End point title	Percentage of Subjects Who Required Rescue Medication

End point description:

Rescue medications were defined as the immunosuppressive (methylprednisolone, dexamethasone and prednisone) therapies. During the course of the study, subject who required rescue therapy was based on the judgement of the study physician. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Day 28

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: percentage of subjects				
number (not applicable)	13.8	15.0	22.6	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Needed Intensive Care Unit (ICU) Care During Study

End point title	Percentage of Subjects Who Needed Intensive Care Unit (ICU) Care During Study

End point description:

Percentage of subjects who needed ICU care until Day 29 were reported for those not in an ICU at baseline. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects

evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline to Day 29

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	98	114	56	
Units: percentage of subjects				
number (not applicable)	11.2	14.9	12.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days of Hospitalisation Among Survivors (Alive Subjects)

End point title	Number of Days of Hospitalisation Among Survivors (Alive Subjects)

End point description:

Number of days of hospitalisation among alive subjects were counted Day 60 since the first dose. LS mean and SE were estimated using the ANCOVA model with treatment group and randomisation strata as fixed effects. Analysis was performed on mITT population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

At Day 60

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	155	75	
Units: days				
least squares mean (standard error)	15.6 (± 0.96)	16.1 (± 0.91)	15.9 (± 1.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-emergent Serious Adverse Events (SAEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a subject who received study drug and did not necessarily had to have a causal relationship with the treatment. Treatment-emergent AEs (TEAEs) were the AEs that developed or worsened or became serious during the TEAE period (from the time of first dose of study drug to the last dose of study drug + 60 days). SAEs were any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-patient hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Analysis was performed on safety population which included all randomised subjects who were treated with the study medication and were analysed according to the actual treatment received.

End point type	Secondary

End point timeframe:

Baseline up to 60 days

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: subjects	42	51	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Major or Opportunistic Bacterial or Fungal Infections

End point title	Number of Subjects With Major or Opportunistic Bacterial or Fungal Infections

End point description:

Major or opportunistic bacterial or fungal infections was considered as an adverse event of special interest (AESI: defined as an AE [serious or non-serious] of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required). Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline up to 60 days

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: subjects	8	15	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 4 Neutropenia and Grade 4 Neutropenia With Concurrent Invasive Infection

End point title	Number of Subjects With Grade 4 Neutropenia and Grade 4 Neutropenia With Concurrent Invasive Infection

End point description:

Grade 4 neutropenia was defined as subjects with absolute neutrophil count (ANC) <500 per cubic millimetre (mm^3). Grade 4 neutropenia with concurrent invasive infection was defined as infections and infestations (in subjects with Grade 4 neutropenia) within 1 week of ANC <500/mm^3 and was considered as an AESI (defined as an AE [serious or non-serious] of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required). Analysis was performed on safety population. Here, 'n' = subjects with available data for each specified category, "0" in 'n' filed signifies that no subjects had Grade 4 neutropenia and therefore were not evaluable and 'CII' represents concurrent invasive infection.

End point type	Secondary

End point timeframe:

Baseline up to 60 days

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: subjects				
Grade 4 neutropenia (n=159,173,84)	3	6	0	
Grade 4 Neutrapenia + CII (n=3,6,0)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade >=2 Infusion Reactions, Grade >=2 Hypersensitivity Reactions and Gastrointestinal Perforation

End point title	Number of Subjects With Grade >=2 Infusion Reactions, Grade >=2 Hypersensitivity Reactions and Gastrointestinal Perforation

End point description:

Grade >=2 (moderate) infusion related reactions (defined as any TEAE signs or symptoms experienced by subjects who received study medication within 24 hours of the start of infusion) and Grade >=2 (moderate) hypersensitivity reactions (anaphylactic reaction, hypersensitivity or angioedema and moderate reactions) were considered as AESI which was defined as an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor was required. Gastrointestinal perforation was defined as formation of a hole through the stomach, large bowel or small intestine. Analysis was performed on safety population.

End point type	Secondary

End point timeframe:

Baseline up to 60 days

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	159	173	84	
Units: subjects				
Grade >=2 Infusion related reactions	1	6	0	
Grade >=2 Hypersensitivity reactions	1	7	0	
Gastrointestinal perforation	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities (PCSA): Hematological Parameter - Hemoglobin, Leukocytes and Platelets

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities (PCSA): Hematological Parameter - Hemoglobin, Leukocytes and Platelets

End point description:

Criteria for PCSA:
• Hemoglobin: less than or equal to (<=) 115 grams per litre (g/L) (male) and <=95 g/L (female); greater than or equal to (>=) 185 g/L (male) and >=165 g/L (female); and decrease from baseline >=20 g/L
• Leukocytes: <3.0*10^9/Litres (L) (Non-Black [NB]) or <2.0*10^9/L (black [B]); >=16.0*10^9/L.
• Platelets: < 100*10^9/L; >=700*10^9/L.
Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 60 days

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	170	84	
Units: subjects				
Hemoglobin <=115 g/L (male) and <=95 g/L (female)	29	34	15	
Hemoglobin >=185 g/L (male) and >=165 g/L (female)	0	0	0	
Hemoglobin decrease from baseline >=20 g/L	32	30	15	
Leukocytes <3.0*10^9/L (NB) or <2.0*10^9/L (B)	19	31	1	
Leukocytes >=16*10^9/L	13	21	6	
Platelets <100*10^9/L	2	7	3	
Platelets >=700*10^9/L	3	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities: Renal Function Parameters

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities: Renal Function Parameters

End point description:

Criteria for PCSA: Creatinine: >=150 micromoles per litre (mcmol/L); >=30% change from baseline; >= 100% change from baseline. Analysis was performed on safety population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline up to 60 days

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	170	84	
Units: subjects				
Creatinine >=150 mcmol/L	15	15	5	
>=30% change from baseline in Creatinine	31	30	10	
>=100% change from baseline in Creatinine	6	7	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities: Liver Function Parameters

End point title	Number of Subjects With Potentially Clinically Significant Laboratory Abnormalities: Liver Function Parameters

End point description:

Criteria for PCSA:
• Alanine Aminotransferase (ALT): >3 upper limit of normal (ULN); >5 ULN; >10 ULN and >20 ULN
• Bilirubin: >1.5 ULN; >2 ULN.
Analysis was performed on safety population. Here, 'number of subjects analysed'=subjects evaluable for this endpoint & ‘n’=subjects with available data for each specified category.

End point type	Secondary

End point timeframe:

Baseline up to 60 days

End point values	Sarilumab 200 mg	Sarilumab 400 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	156	169	84	
Units: subjects				
ALT >3 ULN (n = 156, 168, 83)	60	63	24	
ALT >5 ULN (n = 156, 168, 83)	28	25	12	
ALT >10 ULN (n = 156, 168, 83)	6	5	3	
ALT >20 ULN (n = 156, 168, 83)	1	0	0	
Bilirubin >1.5 ULN (n = 156, 169, 84)	5	4	4	
Bilirubin >2 ULN (n = 156, 169, 84)	4	2	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the time of first dose of study drug up to 60 days regardless of seriousness or relationship to study drug.

Adverse event reporting additional description:

Reported AEs and deaths were TEAEs that developed/worsened in grade or became serious during 'TEAE period' (from the time of first dose of study drug to the last dose of study drug + 60 days). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Sarilumab 200 mg

Reporting group description:

Sarilumab 200 mg, single dose of IV injection on Day 1. Subjects could receive a second dose of sarilumab 200 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Reporting group title	Sarilumab 400 mg

Reporting group description:

Sarilumab 400 mg, single dose of IV injection on Day 1. Subjects could receive a second dose of sarilumab 400 mg 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Reporting group title	Placebo

Reporting group description:

Placebo (for sarilumab), single dose of IV injection on Day 1. Subjects could receive a second dose of placebo (for sarilumab) 24 to 48 hours after the first dose if first and any one of last three criteria was met as compared to Day 1 (as per following protocol amendment 2 [dated 08-Apr-2020]):
•Benefit risk assessment by the investigator favored the administration of another dose of study drug without compromising safety and
•Increase/recurrence of fever or
•Increase/no change in FiO2 requirement or
•Required vasopressors, ECMO or development of multi-organ dysfunction.

Serious adverse events	Sarilumab 200 mg	Sarilumab 400 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	42 / 159 (26.42%)	51 / 173 (29.48%)	20 / 84 (23.81%)
number of deaths (all causes)	17	18	9
number of deaths resulting from adverse events	0	2	0

Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 159 (0.63%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertensive Crisis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Occlusion			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis Superficial			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vena Cava Thrombosis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous Thrombosis Limb			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Hyperthermia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	2 / 159 (1.26%)	3 / 173 (1.73%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 3
Physical Deconditioning			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Death			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			
subjects affected / exposed	0 / 159 (0.00%)	4 / 173 (2.31%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoxia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising Pneumonia			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumomediastinum			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumothorax			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax Spontaneous			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	1 / 159 (0.63%)	2 / 173 (1.16%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory Arrest			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory Distress			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	6 / 159 (3.77%)	5 / 173 (2.89%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 6	1 / 5	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 1
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	4 / 159 (2.52%)	3 / 173 (1.73%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	2 / 4	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur Fracture			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion Related Reaction			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 159 (0.63%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intracardiac Thrombus			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulseless Electrical Activity			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Brain Oedema			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Carotid Artery Thrombosis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular Accident			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoxic-Ischaemic Encephalopathy			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	2 / 159 (1.26%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood Loss Anaemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 159 (0.63%)	3 / 173 (1.73%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Entropion			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Perforation			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-Abdominal Haematoma			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Megacolon			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Steatosis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 159 (0.63%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis Acute			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Injury			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	2 / 159 (1.26%)	4 / 173 (2.31%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	0 / 159 (0.00%)	2 / 173 (1.16%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess Limb			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial Infection			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Covid-19 Pneumonia			
subjects affected / exposed	11 / 159 (6.92%)	4 / 173 (2.31%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 11	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 6	0 / 3	0 / 1
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis Klebsiella			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Respiratory Tract Infection Fungal			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Peritonitis			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 159 (0.63%)	6 / 173 (3.47%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 1	4 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Bacterial			
subjects affected / exposed	1 / 159 (0.63%)	3 / 173 (1.73%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 0
Pneumonia Klebsiella			
subjects affected / exposed	1 / 159 (0.63%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	0 / 159 (0.00%)	0 / 173 (0.00%)	1 / 84 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	4 / 159 (2.52%)	4 / 173 (2.31%)	2 / 84 (2.38%)
occurrences causally related to treatment / all	0 / 4	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 1
Soft Tissue Infection			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal Sepsis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic Bacterial Infection			

subjects affected / exposed	0 / 159 (0.00%)	2 / 173 (1.16%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic Candida			
subjects affected / exposed	0 / 159 (0.00%)	2 / 173 (1.16%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertriglyceridaemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 159 (0.00%)	1 / 173 (0.58%)	0 / 84 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Sarilumab 200 mg	Sarilumab 400 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 159 (35.85%)	68 / 173 (39.31%)	14 / 84 (16.67%)
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	48 / 159 (30.19%)	58 / 173 (33.53%)	14 / 84 (16.67%)
occurrences (all)	48	59	14
Aspartate Aminotransferase			

Increased			
subjects affected / exposed	11 / 159 (6.92%)	15 / 173 (8.67%)	0 / 84 (0.00%)
occurrences (all)	11	16	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	11 / 159 (6.92%)	13 / 173 (7.51%)	0 / 84 (0.00%)
occurrences (all)	11	13	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2020	• Clarified statistical analysis:multiplicity control. • Changed Phase 2 primary endpoint (PE):time to resolution of fever for at least 48 hours without antipyretics/until discharge, whichever was sooner. • Added Day 15 in Phase 3 PE. • Added Phase 2 & Phase 3 PE:proportion of subjects required rescue medication in 28-day period. • Screening partial to severe subjects until 100 subjects reached Day 15, later screening considered of same/greater severity. • Stratified 'systemic' corticosteroids to add systemic corticosteroid use. • Modified Phase 3 sample size to re-estimate based on Phase 2 results. • Modified accrual duration to 3 months. • Clarified starting time for time-to-fever-resolution analysis in Phase 2 primary analysis. • Added cut-off of Phase 2 analyses & multiplicity control. • Inclusion criteria:clarified positive SARS-CoV-2-test. • Blood samples collection:clarified central analysis of SARS-CoV-2 viral load; not used for determining inclusion criteria. • Clarified early-discontinued subjects had to complete end of study visit, if possible. • Clarified all AEs and maximum body temperature (any time period/window) to be recorded in CRF. • Modified benefit/risk:review of safety data by data monitoring committee after dosing of 1st 12 subjects was not required prior to enrolling additional subjects. • Inclusion criterion:removed 'fever' in pneumonia definition. • Modified inclusion criterion:regional variability in SARS-CoV-2 testing recommendations. • Modified exclusion criterion:In opinion of Investigator, unlikely to survive after 48 hours/unlikely to remain at investigational site beyond 48 hours. • Added blinding breaking rules. • Added in rescue therapy to mitigate risk of potential lack of benefit from investigational intervention. • Changed 'Limited Physical Examination' to 'Targeted Physical Examination'; added consciousness in NEWS2. • Phase 3 PE:added detailed sample size determination. • Efficacy PE:fever definition.

08 April 2020	• Changed protocol's title: An adaptive phase 3, randomised, double-blind, placebocontrolled study assessing efficacy and safety of sarilumab for hospitalised subjects with COVID19'. • Changed primary efficacy endpoint: time to improvement of 2 points in clinical status assessment from baseline using 7-point ordinal scale. • Added key secondary efficacy endpoint: percent of subjects alive at Day 29' and 'proportion of subjects with 1 point improvement from baseline in clinical status assessment at Days 4, 7,15, 21, and 29 using 7-point ordinal scale'. • Removed screening of severe subjects until almost 100 subjects had reached Day 15, later screening could be considered for subjects of same/greater severity. • Added 2nd dose of study treatment, as optimal dose of sarilumab IV for subjects with severe/critical COVID-19 was unknown. • Removed and stratified severity category of multi-system organ dysfunction. • Clarified interim analysis:performed when approximately 50% of total planned number of subjects (~200) had reached Day 15 to obtain an understanding of possible drug effect in population under study. • Clarified urinalysis and urine culture results only requested if available. • Clarified exclusion criterion:subjects requiring extracorporeal life support, vasopressors/renal replacement therapy were excluded. • Removed sarilumab as rescue therapy. • Clarified rescue therapy could be given 48 hours after last infusion. • Defined infusion related reactions: any signs or symptoms experienced by subjects who received IMP within 24 hours of the start of infusion. • Modified SAE definition as 'Requires a "new" inpatient hospitalisation/prolongation of existing hospitalisation'. • Added medically important events intended to serve as guideline for determining medically important event. • Corrected protocol amendment: use of immunosuppressive therapy following infusion of study drug, besides corticosteroids and anti-malarial medication.
29 April 2020	• Removed requirement in the Synopsis and clinical Laboratory tests that the interim analysis required data up to Day 15. • Clarified that pharmacokinetic sample collection for Day 2 and Day 3. • Removed 'optional' for the serum sIL-6R in footnote 24 of the schedule of activities. • Changed 'multisystem organ dysfunction' to 'multi-organ dysfunction' (Benefit/Risk Assessment) to align with the publication where it is described. • Clarified that IDMC would actively monitor interim data, and also make recommendations pertaining to the eligible population throughout the course of the study. • Removed use of vasopressors as a factor to be considered for selection criterion as vasopressors were also used by critical subjects and not primarily subjects with multiorgan disease (who are excluded). • Clarified the scope of adaptations that the Sponsor could make based on the interim analysis results.
11 June 2020	• Closed enrollment to the sarilumab 200 mg IV arm. • Clarified that no changes in urinalysis and urine culture results, serum IL-6, and AEs were made to the collection schedule. • Modified exclusion criterion to clarify that oral corticosteroids were a type of systemic corticosteroids. • Removed the following bullet point (Definition of AE) as it was duplicated in error: "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • Removed following bullet point (Definition of AE) as the information was contradictory to that of a previous bullet point: The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constituted an AE or SAE. • Added tables for assessment of intensity for infusion related reactions, hypersensitivity reactions, and neutropenia (recording and follow-up of AE and/or SAE) to provide guidance to the Investigator. • Added guidance for the follow-up of AESIs of ALT increase and Grade 4 Neutropenia (recording and follow-up of AE and/or SAE) to provide guidance to the Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported