



Clinical trial results:

An open-label, multi-centre, randomised trial comparing different doses of single-dose tocilizumab in adults with severe, non-critical, PCR-confirmed COVID-19 infection with evidence of progressive decline in respiratory function and evolving systemic inflammation on time to intubation, non-invasive ventilation and/or all-cause mortality

Summary

EudraCT number	2020-001767-86
Trial protocol	IE
Global end of trial date	04 November 2022

Results information

Result version number	v1 (current)
This version publication date	07 January 2026
First version publication date	07 January 2026

Trial information

Trial identification

Sponsor protocol code	COVIRL-002
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Belfield, Dublin, Ireland, Dublin 4
Public contact	UCD Clinical Research Center, University College Dublin, crc.monitoring@ucd.ie
Scientific contact	Centre for Experimental Pathogen Host Research, University College Dublin, cephr@ucd.ie

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	07 December 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2022
Global end of trial reached?	Yes
Global end of trial date	04 November 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the safety and efficacy of standard dose versus low dose tocilizumab in adults with severe, non-critical, PCR-confirmed COVID-19 infection with evidence of progressive decline in respiratory function and evolving systemic inflammation on time to intubation, non-invasive ventilation and/or all-cause mortality.

Protection of trial subjects:

This trial was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

All subjects provided informed consent before undergoing any trial related procedures.

The trial was reviewed and approved by the Competent Authorities and the local Research Ethics Committees (REC).

An independent Data and Safety Monitoring Board (DSMB) was established to perform ongoing safety surveillance and to perform interim analyses on the study data. The DSMB acts as an independent committee, composed of a minimum of three members; at least two are clinicians not involved in the trial but with experience and expertise in clinical trials and / or biostatistics; at least one member is a clinician with expertise in infectious diseases.

Administration of the IMP was given in a hospital setting with appropriate resuscitation facility and staff available in the event of an emergency.

Background therapy:

Eligible participants will be randomised (1:1) to receive either standard of care alone or standard of care plus single dose (8mg/kg, maximum 800mg) intravenous tocilizumab infused over 60 minutes.

Evidence for comparator: -

Actual start date of recruitment	13 April 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 76
Worldwide total number of subjects	76
EEA total number of subjects	76

Notes:

Subjects enrolled per age group

In utero	0
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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)	42
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started in Ireland in May 2020. 76 subjects were recruited, the first on 18/09/2020 and the last on 13/12/2021. A total of 75 were randomised (1 screen failure)

Pre-assignment

Screening details:

Study population comprised adults with PCR-confirmed COVID-19 infection requiring admission to hospital.

Period 1

Period 1 title	Intention to Treat (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

N/A

Arms

Are arms mutually exclusive?	Yes
Arm title	SOC + TC

Arm description:

Standard of Care + Tocilizumab 8mg/kg

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

Dosage and administration details:

After dilution, tocilizumab is administered as an intravenous infusion over 1 hour. In patients ≥ 30 kg tocilizumab should be diluted to a final volume of 100 mL with sterile, nonpyrogenic sodium chloride 9 mg/mL (0.9%) solution for injection using aseptic technique.

Arm title	Standard of care
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Arm description:

Standard of Care (SOC)

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1 ^[1]	SOC + TC	Standard of care
Started	38	37
Completed	32	26
Not completed	6	11
Adverse event, serious fatal	5	3
Consent withdrawn by subject	-	2

Transfer to another health facility	-	2
Lost to follow-up	1	4

Notes:

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

Justification: Enrolled population includes all participants who formally consented to participate in the study, while the baseline period only consists of the ITT population (i.e. randomised)

Baseline characteristics

Reporting groups

Reporting group title	SOC + TC
Reporting group description:	
Standard of Care + Tocilizumab 8mg/kg	
Reporting group title	Standard of care
Reporting group description:	
Standard of Care (SOC)	

Reporting group values	SOC + TC	Standard of care	Total
Number of subjects	38	37	75
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age			
Units: years			
median	61.0	65.1	
inter-quartile range (Q1-Q3)	50.6 to 70.7	53.8 to 72.0	-
Gender categorical			
Units: Subjects			
Female	15	15	30
Male	23	22	45
Race			
Units: Subjects			
White	30	31	61
Asian or Asian Irish	5	3	8
Black or Black Irish	1	1	2
Other	2	1	3
Not reported	0	1	1
Smoking status			
Units: Subjects			
Ex-smoker	12	15	27
Non-smoker	24	21	45
Unknown	2	1	3
Electrocardiogram results			
Units: Subjects			
Abnormal, clinically significant	2	5	7

Abnormal, not clinically significant	7	7	14
Within normal limits	29	25	54
Obesity			
Co-existing condition			
Units: Subjects			
Present	18	20	38
Absent	20	17	37
Diabetes without complications			
Co-existing conditions			
Units: Subjects			
Present	7	9	16
Absent	31	28	59
Chronic cardiac disease			
Co-existing condition			
Units: Subjects			
Present	6	9	15
Absent	32	28	60
BMI			
Body Mass Index			
Units: kg/cm ²			
median	30.4	31.4	-
inter-quartile range (Q1-Q3)	26.9 to 37.9	26.8 to 38.1	-
Ferritin			
Units: microg/L			
median	1218	1149	-
inter-quartile range (Q1-Q3)	794 to 2059	576.5 to 1753	-
Fibrinogen			
Units: g/L			
median	4.93	5.50	-
inter-quartile range (Q1-Q3)	4.37 to 6.36	5.05 to 6.70	-
Troponin T			
Units: ng/L			
median	6.00	8.00	-
inter-quartile range (Q1-Q3)	5.00 to 12.00	5.00 to 13.00	-
D-dimer			
Units: microg FEU/mL			
median	0.85	1.11	-
inter-quartile range (Q1-Q3)	0.63 to 1.87	0.77 to 2.33	-
C-Reactive Protein			
Units: mg/L			
median	116.3	139.6	-
inter-quartile range (Q1-Q3)	72.70 to 137.9	107.3 to 168.5	-
Lactate dehydrogenase			
Units: U/L			
median	455.0	479.0	-
inter-quartile range (Q1-Q3)	387.0 to 497.0	408.5 to 582.5	-
Interleukin-6			
Units: pg/mL			
median	35.45	23.60	-
inter-quartile range (Q1-Q3)	7.30 to 85.50	11.60 to 53.70	-

End points

End points reporting groups

Reporting group title	SOC + TC
Reporting group description: Standard of Care + Tocilizumab 8mg/kg	
Reporting group title	Standard of care
Reporting group description: Standard of Care (SOC)	

Primary: Time to a composite primary endpoint of progression to intubation and ventilation, non-invasive ventilation or death

End point title	Time to a composite primary endpoint of progression to intubation and ventilation, non-invasive ventilation or death
End point description: Time from randomisation to the first occurrence of any of the event: intubation and ventilation, non-invasive ventilation or death	
End point type	Primary
End point timeframe: 28 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: 1.0	19	11		

Attachments (see zip file)	eudract_surv.png
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Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Kaplan-Meier methods with the log-rank test to compare treatment groups. Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with treatment group and stratification for site as covariates.	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.97

Secondary: Prevalence of new SAE at day 8

End point title	Prevalence of new SAE at day 8
End point description:	
End point type	Secondary
End point timeframe:	
8 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: Count	22	13		

Statistical analyses

Statistical analysis title	Difference in proportion with new SAE at day 8
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Fisher exact
Parameter estimate	proportion
Confidence interval	
level	95 %
sides	2-sided

Secondary: Time to a composite primary endpoint of progression to intubation and ventilation, non-invasive ventilation or death at 8 days

End point title	Time to a composite primary endpoint of progression to intubation and ventilation, non-invasive ventilation or death at 8 days
End point description:	
Time from randomisation to the first occurrence of any of the event: intubation and ventilation, non-invasive ventilation or death at 8 days	
End point type	Secondary

End point timeframe:

8

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: 1.0	17	11		

Statistical analyses

Statistical analysis title	Time to event analysis - Secondary endpoint
Statistical analysis description:	
Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with treatment group and stratification for site as covariates.	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	3.59

Secondary: Time to a composite primary endpoint of progression to intubation and ventilation, non-invasive ventilation or death at 14 days

End point title	Time to a composite primary endpoint of progression to intubation and ventilation, non-invasive ventilation or death at 14 days
End point description:	
Time from randomisation to the first occurrence of any of the event: intubation and ventilation, non-invasive ventilation or death at 14 days	
End point type	Secondary
End point timeframe:	
14 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: 1.0	19	11		

Statistical analyses

Statistical analysis title	Time to event analysis - Secondary endpoint
Statistical analysis description:	
Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with treatment group and stratification for site as covariates.	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.97

Secondary: Survival at 8 days

End point title	Survival at 8 days
End point description:	
Overall survival - time from randomisation to death. Any patients lost to follow-up or still alive at 8 days are censored	
End point type	Secondary
End point timeframe:	
8 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: 1.0	2	2		

Statistical analyses

Statistical analysis title	Time to event analysis - Secondary endpoint
Statistical analysis description:	
Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with treatment group and stratification for site as covariates.	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.947
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	6.64

Secondary: Survival at 14 days

End point title	Survival at 14 days
End point description:	
Overall survival - time from randomisation to death. Any patients lost to follow-up or still alive at 14 days are censored	
End point type	Secondary
End point timeframe:	
14 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: 1.0	3	2		

Statistical analyses

Statistical analysis title	Time to event analysis - Secondary endpoint
Statistical analysis description:	
Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with treatment group and stratification for site as covariates.	
Comparison groups	SOC + TC v Standard of care

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.723
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	8.27

Secondary: Survival at 28 days

End point title	Survival at 28 days
End point description:	
Overall survival - time from randomisation to death. Any patients lost to follow-up or still alive at 28 days are censored	
End point type	Secondary
End point timeframe:	
28 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: 1.0	5	2		

Statistical analyses

Statistical analysis title	Time to event analysis - Secondary endpoint
Statistical analysis description:	
Hazard ratios and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with treatment group and stratification for site as covariates.	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.28

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	11.76

Secondary: Incidence of intercurrent bacterial sepsis (positive blood culture) or septic shock (regardless of causative agent)

End point title	Incidence of intercurrent bacterial sepsis (positive blood culture) or septic shock (regardless of causative agent)
End point description:	
End point type	Secondary
End point timeframe:	
Overall (28 days)	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: 1.0				
Present	1	2		

Statistical analyses

Statistical analysis title	Incidence of intercurrent bacterial sepsis/septic
Comparison groups	Standard of care v SOC + TC
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Fisher exact

Secondary: Change from baseline in C-Reactive Protein (mg/L) at 8 days

End point title	Change from baseline in C-Reactive Protein (mg/L) at 8 days
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline in C-Reactive Protein (mg/L) to 8 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	26		
Units: mg/L				
least squares mean (confidence interval 95%)	-117.61 (-132.23 to -103.46)	-91.97 (-106.71 to -77.23)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-25.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.12
upper limit	-8.18

Secondary: Change from baseline in C-Reactive Protein (mg/L) at 14 days

End point title	Change from baseline in C-Reactive Protein (mg/L) at 14 days
End point description:	
End point type	Secondary
End point timeframe:	
14 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: mg/L				
least squares mean (confidence interval 95%)	-113.61 (-132.23 to -95.00)	-78.48 (-98.94 to -58.01)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description: ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-35.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.37
upper limit	-10.89

Secondary: Change from baseline in C-Reactive Protein (mg/L) at 28 days

End point title	Change from baseline in C-Reactive Protein (mg/L) at 28 days
End point description:	
End point type	Secondary
End point timeframe: 28 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	22		
Units: mg/L				
least squares mean (confidence interval 95%)	-106.69 (-126.21 to -87.18)	-101.89 (-124.22 to -79.56)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description: ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.2
upper limit	21.59

Secondary: Change from baseline in Ferritin (microg/L) at 8 days

End point title	Change from baseline in Ferritin (microg/L) at 8 days
End point description:	
End point type	Secondary
End point timeframe: 8 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	24		
Units: microg/L				
least squares mean (confidence interval 95%)	-639.92 (-1157.62 to -122.21)	-851.96 (-1368.53 to -335.39)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description: ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates	
Comparison groups	SOC + TC v Standard of care

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	212.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-445.43
upper limit	869.53

Secondary: Change from baseline in Ferritin (microg/L) at 14 days

End point title	Change from baseline in Ferritin (microg/L) at 14 days
End point description:	
End point type	Secondary
End point timeframe:	
14 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: microg/L				
least squares mean (confidence interval 95%)	-1190.76 (-1457.05 to -924.47)	-1271.51 (-1551.83 to -991.19)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	80.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-275.72
upper limit	437.22

Secondary: Change from baseline in Ferritin (microg/L) at 28 days

End point title	Change from baseline in Ferritin (microg/L) at 28 days
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End point description:

End point type	Secondary
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End point timeframe:

28 days

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	21		
Units: microg/L				
least squares mean (confidence interval 95%)	-1238.51 (-1444.29 to -1032.74)	-1092.01 (-13209.91 to -863.1)		

Statistical analyses

Statistical analysis title	ANCOVA
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Statistical analysis description:

ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates

Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-146.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-421.41
upper limit	128.39

Secondary: Change from baseline in D-dimer (microg FEU/ml) at 8 days

End point title	Change from baseline in D-dimer (microg FEU/ml) at 8 days
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End point description:

End point type	Secondary
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End point timeframe:

8 days

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	21		
Units: microg FEU/ml				
least squares mean (confidence interval 95%)	0.13 (-0.88 to 1.14)	0.15 (-0.85 to 1.15)		

Statistical analyses

Statistical analysis title	ANCOVA
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Statistical analysis description:

ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates

Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	1.29

Secondary: Change from baseline in D-dimer (microg FEU/ml) at 14 days

End point title	Change from baseline in D-dimer (microg FEU/ml) at 14 days
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End point description:

End point type	Secondary
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End point timeframe:

14 days

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	20		
Units: microg FEU/ml				
least squares mean (confidence interval 95%)	-0.9 (-1.24 to -0.56)	-0.65 (-1.01 to -0.28)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.22

Secondary: Change from baseline in D-dimer (microg FEU/ml) at 28 days

End point title	Change from baseline in D-dimer (microg FEU/ml) at 28 days
End point description:	
End point type	Secondary
End point timeframe:	
28 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	18		
Units: microg FEU/ml				
least squares mean (confidence interval 95%)	-0.79 (-1.51 to -0.07)	-0.7 (-1.46 to 0.08)		

Statistical analyses

Statistical analysis title	ANCOVA
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Statistical analysis description:

ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates

Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	0.87

Secondary: Change from baseline in Lactate dehydrogenase (U/L) at 8 days

End point title	Change from baseline in Lactate dehydrogenase (U/L) at 8 days
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End point description:

End point type	Secondary
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End point timeframe:

8 days

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	20		
Units: U/L				
least squares mean (confidence interval 95%)	-136.07 (-202.47 to -69.67)	-115.21 (-187.5 to -42.92)		

Statistical analyses

Statistical analysis title	ANCOVA
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Statistical analysis description:

ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates

Comparison groups	SOC + TC v Standard of care
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Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-20.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-108.26
upper limit	66.53

Secondary: Change from baseline in Lactate dehydrogenase (U/L) at 14 days

End point title	Change from baseline in Lactate dehydrogenase (U/L) at 14 days
End point description:	
End point type	Secondary
End point timeframe:	14 days

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: U/L				
least squares mean (confidence interval 95%)	-202.62 (-234.53 to -170.72)	-209.61 (-241.39 to -177.83)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
	ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	6.99

Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.16
upper limit	47.13

Secondary: Change from baseline in Lactate dehydrogenase (U/L) at 28 days

End point title	Change from baseline in Lactate dehydrogenase (U/L) at 28 days
End point description:	
End point type	Secondary
End point timeframe:	
28 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	18		
Units: U/L				
least squares mean (confidence interval 95%)	-229.97 (-265.52 to -194.41)	-240.21 (-279.21 to -201.21)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
ANCOVA model with change from baseline as outcome and treatment, baseline value and site as covariates	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	10.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.77
upper limit	58.25

Secondary: Change from baseline in Interleukin - 6 (pg/ml) at 8 days

End point title	Change from baseline in Interleukin - 6 (pg/ml) at 8 days
End point description:	
End point type	Secondary
End point timeframe:	
8 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	13		
Units: pg/ml				
least squares mean (confidence interval 95%)	214.71 (38.01 to 391.41)	-43.67 (-227.41 to 139.68)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
ANCOVA model with change from baseline as outcome and treatment, baseline value	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	258.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	516.63

Secondary: Change from baseline in Interleukin - 6 (pg/ml) at 14 days

End point title	Change from baseline in Interleukin - 6 (pg/ml) at 14 days
End point description:	
End point type	Secondary
End point timeframe:	
14 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	15		
Units: pg/ml				
least squares mean (confidence interval 95%)	232.12 (62.76 to 401.48)	-33.84 (-219.58 to 151.89)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	265.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.06
upper limit	518.87

Secondary: Change from baseline in Interleukin - 6 (pg/ml) at 28 days

End point title	Change from baseline in Interleukin - 6 (pg/ml) at 28 days
End point description:	
End point type	Secondary
End point timeframe:	
28 days	

End point values	SOC + TC	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	15		
Units: pg/ml				
least squares mean (confidence interval 95%)	-4 (-47.62 to 39.62)	-43.88 (-94.47 to 6.71)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description:	
ANCOVA model with change from baseline as outcome and treatment, baseline value	
Comparison groups	SOC + TC v Standard of care
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	39.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.9
upper limit	107.67

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of Informed Consent up to 90 days after the last dose of the study drug has been received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	SOC + TC
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Reporting group description:

Standard of Care + Tocilizumab 8mg/kg

Reporting group title	Standard of Care
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Reporting group description:

Standard of Care (SOC)

Serious adverse events	SOC + TC	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 38 (63.16%)	15 / 37 (40.54%)	
number of deaths (all causes)	5	2	
number of deaths resulting from adverse events	5	2	
Vascular disorders			
Peripheral artery occlusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Mechanical ventilation			
subjects affected / exposed	19 / 38 (50.00%)	10 / 37 (27.03%)	
occurrences causally related to treatment / all	0 / 21	0 / 10	
deaths causally related to treatment / all	0 / 4	0 / 1	
Intensive care			
subjects affected / exposed	11 / 38 (28.95%)	6 / 37 (16.22%)	
occurrences causally related to treatment / all	0 / 11	0 / 6	
deaths causally related to treatment / all	0 / 4	0 / 1	
Hospitalisation			

subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (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	0 / 38 (0.00%)	1 / 37 (2.70%)	
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 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumopericardium			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (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 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seizure like phenomena			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	4 / 38 (10.53%)	3 / 37 (8.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumomediastinum			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Skin and subcutaneous tissue disorders Subcutaneous emphysema	subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders Delirium	subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
	occurrences causally related to treatment / all	0 / 0	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder	subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders Acute kidney injury	subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations Pneumonia	subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	
	occurrences causally related to treatment / all	0 / 1	0 / 1	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection	subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration	subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
	occurrences causally related to treatment / all	0 / 1	0 / 0	
	deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia bacterial				

subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SOC + TC	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 38 (60.53%)	16 / 37 (43.24%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 38 (7.89%)	3 / 37 (8.11%)	
occurrences (all)	3	3	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 38 (7.89%)	1 / 37 (2.70%)	
occurrences (all)	3	1	
Chest X-ray abnormal			
subjects affected / exposed	2 / 38 (5.26%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Lipids abnormal			
subjects affected / exposed	2 / 38 (5.26%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Transaminases increased			
subjects affected / exposed	3 / 38 (7.89%)	1 / 37 (2.70%)	
occurrences (all)	3	1	
Liver function test abnormal			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	
occurrences (all)	3	1	
Blood cholesterol increased			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	

Liver function test increased subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0	
Troponin increased subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0	
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 37 (2.70%) 1	
Surgical and medical procedures Mechanical ventilation subjects affected / exposed occurrences (all)	21 / 38 (55.26%) 23	10 / 37 (27.03%) 10	
Intensive care subjects affected / exposed occurrences (all)	11 / 38 (28.95%) 11	6 / 37 (16.22%) 6	
Hospitalisation subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 37 (5.41%) 2	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	2 / 37 (5.41%) 2	
Bradycardia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 37 (2.70%) 1	
General disorders and administration site conditions Chest pain subjects affected / exposed occurrences (all)	1 / 38 (2.63%) 1	3 / 37 (8.11%) 3	
Fatigue subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 37 (2.70%) 1	
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	1 / 37 (2.70%) 1	
Mouth ulceration subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	1 / 37 (2.70%) 1	
Respiratory, thoracic and mediastinal disorders Pulmonary embolism subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 4	3 / 37 (8.11%) 3	
Dyspnoea subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0	
Haemoptysis subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	2 / 37 (5.41%) 2	
Hypoxia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	0 / 37 (0.00%) 0	
Hepatobiliary disorders Hypertransaminasaemia subjects affected / exposed occurrences (all)	5 / 38 (13.16%) 5	0 / 37 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 38 (0.00%) 0	4 / 37 (10.81%) 4	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 6	2 / 37 (5.41%) 2	
Metabolism and nutrition disorders Hypernatraemia subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	2 / 37 (5.41%) 6	
Hyperglycaemia			

subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Hyponatraemia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial planned for two phases completed only Phase 1. It was terminated prematurely, in line with the advice from the Data Safety Monitoring Board, resulting in a smaller sample size that limits power and interpretation.

Notes: