



Clinical trial results:

A phase III, randomized, double-blind, multicenter study to evaluate the efficacy and safety of remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized patients with severe COVID-19 pneumonia

Summary

EudraCT number	2020-002275-34
Trial protocol	ES
Global end of trial date	08 March 2021

Results information

Result version number	v1 (current)
This version publication date	16 March 2022
First version publication date	16 March 2022

Trial information

Trial identification

Sponsor protocol code	WA42511
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04409262
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hoffmann-La Roche
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 April 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of tocilizumab plus remdesivir (TCZ+RDV) compared with placebo plus remdesivir (PBO+RDV) in hospitalized patients with severe COVID-19 pneumonia.

Protection of trial subjects:

All subjects were required to sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 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	Brazil: 154
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	United States: 432
Worldwide total number of subjects	649
EEA total number of subjects	14

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)	400
From 65 to 84 years	238

85 years and over	11
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with severe COVID-19 pneumonia

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Remdesivir + Tocilizumab (RDV+TCZ)
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Arm description:

Participants were to receive a 200 mg intravenous (IV) loading dose of RDV, followed by one infusion of TCZ on Day 1. Participants were then to be given a 100 mg once daily IV maintenance dose of RDV from Days 2-10, with discontinuation at discharge whether or not 10 days of RDV dosing were completed. One additional infusion of TCZ was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.

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

Dosage and administration details:

200 mg IV loading dose, followed by a 100 mg once-daily IV maintenance dose from Days 2-10.

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

Dosage and administration details:

One IV TCZ infusion at a dose of 8 mg/kg to a maximum of 800 mg per dose. One additional infusion of TCZ was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.

Arm title	Remdesivir + Placebo (RDV+Placebo)
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Arm description:

Participants were to receive a 200 mg intravenous (IV) loading dose of RDV, followed by one infusion of PBO on Day 1. Participants were then to be given a 100 mg once daily IV maintenance dose of RDV from Days 2-10, with discontinuation at discharge whether or not 10 days of RDV dosing were completed. One additional infusion of PBO was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.

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

Dosage and administration details:

One IV infusion of placebo. One additional infusion of IV placebo was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.

Investigational medicinal product name	Remdesivir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg IV loading dose, followed by a 100 mg once-daily IV maintenance dose from Days 2-10

Number of subjects in period 1	Remdesivir + Tocilizumab (RDV+TCZ)	Remdesivir + Placebo (RDV+Placebo)
Started	434	215
Completed	300	140
Not completed	134	75
Consent withdrawn by subject	10	5
Adverse Event	2	-
Death	97	55
Lost to follow-up	23	12
Lack of Staff	1	-
Protocol deviation	1	3

Baseline characteristics

Reporting groups

Reporting group title	Remdesivir + Tocilizumab (RDV+TCZ)
Reporting group description:	
Participants were to receive a 200 mg intravenous (IV) loading dose of RDV, followed by one infusion of TCZ on Day 1. Participants were then to be given a 100 mg once daily IV maintenance dose of RDV from Days 2-10, with discontinuation at discharge whether or not 10 days of RDV dosing were completed. One additional infusion of TCZ was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.	
Reporting group title	Remdesivir + Placebo (RDV+Placebo)
Reporting group description:	
Participants were to receive a 200 mg intravenous (IV) loading dose of RDV, followed by one infusion of PBO on Day 1. Participants were then to be given a 100 mg once daily IV maintenance dose of RDV from Days 2-10, with discontinuation at discharge whether or not 10 days of RDV dosing were completed. One additional infusion of PBO was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.	

Reporting group values	Remdesivir + Tocilizumab (RDV+TCZ)	Remdesivir + Placebo (RDV+Placebo)	Total
Number of subjects	434	215	649
Age categorical Units: Subjects			
Adults (18-64 years)	259	141	400
From 65-84 years	167	71	238
85 years and over	8	3	11
Age continuous Units: years			
arithmetic mean	60.1	58.2	
standard deviation	± 13.3	± 13.6	-
Gender categorical Units: Subjects			
Female	167	73	240
Male	267	142	409
Race Units: Subjects			
American Indian or Alaska Native	4	4	8
Asian	17	5	22
Native Hawaiian or Other Pacific Islander	7	3	10
Black or African American	52	20	72
White	282	154	436
More than one race	9	2	11
Unknown or Not Reported	63	27	90
Ethnicity Units: Subjects			
Hispanic or Latino	209	125	334
Not Hispanic or Latino	208	88	296
Unknown or Not Reported	17	2	19

End points

End points reporting groups

Reporting group title	Remdesivir + Tocilizumab (RDV+TCZ)
Reporting group description: Participants were to receive a 200 mg intravenous (IV) loading dose of RDV, followed by one infusion of TCZ on Day 1. Participants were then to be given a 100 mg once daily IV maintenance dose of RDV from Days 2-10, with discontinuation at discharge whether or not 10 days of RDV dosing were completed. One additional infusion of TCZ was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.	
Reporting group title	Remdesivir + Placebo (RDV+Placebo)
Reporting group description: Participants were to receive a 200 mg intravenous (IV) loading dose of RDV, followed by one infusion of PBO on Day 1. Participants were then to be given a 100 mg once daily IV maintenance dose of RDV from Days 2-10, with discontinuation at discharge whether or not 10 days of RDV dosing were completed. One additional infusion of PBO was allowed 8-24 hours after the first for participants with sustained fever or clinically significant worsening of signs or symptoms.	
Subject analysis set title	Remdesivir + Placebo (RDV+Placebo) - mITT population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT population included all randomized participants who received any amount of TCZ or placebo (PBO), with participants grouped according to treatment assigned at randomization.	
Subject analysis set title	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The mITT population included all randomized participants who received any amount of TCZ or placebo (PBO), with participants grouped according to treatment assigned at randomization.	
Subject analysis set title	Remdesivir + Placebo (RDV+Placebo) - safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis population consisted of all participants who received any amount of study medication (RDV and/or TCZ/PBO). Participants were grouped according to the treatment received rather than by the treatment assigned at randomization. Participants that only received RDV and did not receive TCZ/PBO were included in the RDV+PBO arm of the safety population.	
Subject analysis set title	Remdesivir + Tocilizumab (RDV+TCZ) - safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis population consisted of all participants who received any amount of study medication (RDV and/or TCZ/PBO). Participants were grouped according to the treatment received rather than by the treatment assigned at randomization. Participants that only received RDV and did not receive TCZ/PBO were included in the RDV+PBO arm of the safety population.	

Primary: Time to hospital discharge or "ready for discharge" up to Day 28

End point title	Time to hospital discharge or "ready for discharge" up to Day 28
End point description: Defined as days from randomization to hospital discharge or "Ready for Discharge" not followed by ordinal scale category >1, hospital readmission or death. Hospital discharge or "Ready for Discharge" is defined as an ordinal score of 1 on the 7-point ordinal scale. Participants who die are censored at Day 28. 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death	
End point type	Primary

End point timeframe:

Up to Day 28

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	430		
Units: days				
median (confidence interval 95%)	14.0 (11.0 to 16.0)	14.0 (12.0 to 15.0)		

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7414
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.965
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.19

Secondary: Time to mechanical ventilation or death up to Day 28

End point title	Time to mechanical ventilation or death up to Day 28
End point description:	Time to Mechanical Ventilation or Death defined as the time from randomization to the first occurrence of death or mechanical ventilation. For participants already on mechanical ventilation at baseline, only death is counted as an event.
End point type	Secondary
End point timeframe:	
Up to Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210 ^[1]	430 ^[2]		
Units: days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[1] - 9999 = endpoint not estimable due to insufficient number of events

[2] - 9999 = endpoint not estimable due to insufficient number of events

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8993
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.34

Secondary: Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 14

End point title	Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 14
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End point description:

Clinical status was assessed by the investigator according to the following ordinal scale categories: 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death

End point type	Secondary
End point timeframe:	
Day 14	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	428 ^[3]		
Units: Percentage of participants				
number (not applicable)				
Category 1	52.4	54.0		
Category 2	1.9	2.6		
Category 3	11.4	8.9		
Category 4	6.7	9.6		
Category 5	6.7	4.9		
Category 6	11.4	10.0		
Category 7	9.5	10.0		

Notes:

[3] - Two participants had no post-baseline clinical status data to Day 14 and were excluded from analysis

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7648
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.44

Secondary: Time to death up to Day 28

End point title	Time to death up to Day 28
End point description:	
Time to death is defined as the time from randomization to death.	
End point type	Secondary
End point timeframe:	
Up to Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210 ^[4]	430 ^[5]		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[4] - 9999 = endpoint not estimable due to insufficient number of events

[5] - 9999 = endpoint not estimable due to insufficient number of events

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7867
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.948
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.39

Secondary: Time to death up to Day 60

End point title	Time to death up to Day 60
End point description:	Time to death is defined as the time from randomization to death.
End point type	Secondary
End point timeframe:	Up to Day 60

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210 ^[6]	430 ^[7]		
Units: Days				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Notes:

[6] - 9999 = endpoint not estimable due to insufficient number of events

[7] - 9999 = endpoint not estimable due to insufficient number of events

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4602
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.23

Secondary: Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status up to Day 28

End point title	Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status up to Day 28
End point description:	
Defined as time from randomization to the time when at least a 2-category improvement in the 7-category ordinal scale is observed. Patients who die are censored at day 28. Clinical status was assessed by the investigator according to the following ordinal scale categories: 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death	
End point type	Secondary
End point timeframe:	
Up to Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	430		
Units: Days				
median (confidence interval 95%)	11.0 (10.0 to 13.0)	12.0 (11.0 to 13.0)		

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8664
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.21

Secondary: Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 7

End point title	Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 7
End point description:	
Clinical status was assessed by the investigator according to the following ordinal scale categories: 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death	
End point type	Secondary
End point timeframe:	
Day 7	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	428 ^[8]		
Units: Percentage of participants				
number (not applicable)				
Category 1	21.9	19.4		
Category 2	4.3	5.6		
Category 3	17.6	20.1		
Category 4	30.0	29.4		
Category 5	9.5	10.0		
Category 6	12.9	12.1		
Category 7	3.8	3.3		

Notes:

[8] - Two participants had no post-baseline clinical status data to Day 7 and were excluded from analysis.

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9569
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.35

Secondary: Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 21

End point title	Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 21
End point description:	Clinical status was assessed by the investigator according to the following ordinal scale categories: 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death
End point type	Secondary
End point timeframe:	
Day 21	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	428 ^[9]		
Units: Percentage of participants				
number (not applicable)				
Category 1	62.4	64.3		
Category 2	1.4	1.2		
Category 3	4.8	4.7		
Category 4	2.9	4.4		
Category 5	6.7	5.6		
Category 6	7.1	5.8		
Category 7	14.8	14.0		

Notes:

[9] - Two participants had no post-baseline clinical status data to Day 21 and were excluded from analysis

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6331
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.52

Secondary: Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 28

End point title	Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 28
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End point description:

Clinical status was assessed by the investigator according to the following ordinal scale categories: 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical

ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death

End point type	Secondary
End point timeframe:	
Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	428 ^[10]		
Units: Percentage of participants				
number (not applicable)				
Category 1	67.1	66.4		
Category 2	1.4	1.4		
Category 3	1.0	3.5		
Category 4	2.9	3.0		
Category 5	4.3	3.7		
Category 6	3.8	3.7		
Category 7	19.5	18.2		

Notes:

[10] - Two participants had no post-baseline clinical status data to Day 28 and were excluded from analysis

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9622
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.4

Secondary: Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 60

End point title	Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Day 60
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End point description:

Clinical status was assessed by the investigator according to the following ordinal scale categories: 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or \leq 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death

End point type	Secondary
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End point timeframe:

Day 60

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	428 ^[11]		
Units: Percentage of participants				
number (not applicable)				
Category 1	70.0	72.2		
Category 2	1.4	0.7		
Category 3	1.0	1.4		
Category 4	1.4	1.6		
Category 5	0.5	0.7		
Category 6	0	0.7		
Category 7	25.7	22.7		

Notes:

[11] - Two participants had no post-baseline clinical status data to Day 60 and were excluded from analysis

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	638
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.64

Secondary: Proportion of participants requiring initiation of mechanical ventilation post-baseline at Day 28 and Day 60 (participants who did not require mechanical ventilation at baseline)

End point title	Proportion of participants requiring initiation of mechanical ventilation post-baseline at Day 28 and Day 60 (participants who did not require mechanical ventilation at baseline)
End point description:	
Day 28: Participants who withdraw or die prior to Day 28 are assumed to have required mechanical ventilation. Participants without mechanical ventilation prior to discharge are assumed not to have required mechanical ventilation unless they die by Day 28, which are counted as an event. Day 60: Participants who withdraw or die prior to Day 60 are assumed to have required mechanical ventilation. Participants without mechanical ventilation prior to discharge are assumed not to have required mechanical ventilation unless they die by Day 60, which are counted as an event.	
End point type	Secondary
End point timeframe:	
Day 28 and Day 60	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	188 ^[12]	371 ^[13]		
Units: Percentage of participants				
number (confidence interval 95%)				
Day 28	29.8 (23.3 to 36.3)	27.5 (23.0 to 32.0)		
Day 60	31.4 (24.7 to 38.0)	28.8 (24.2 to 33.5)		

Notes:

[12] - Analysis population included only participants not on mechanical ventilation at baseline

[13] - Analysis population included only participants not on mechanical ventilation at baseline

Statistical analyses

Statistical analysis title	Day 60
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5494
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	5.6

Statistical analysis title	Day 28
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	559
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5915
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	5.9

Secondary: Proportion of participants who are alive and free of respiratory failure at Day 28 and Day 60 (participants requiring mechanical ventilation at baseline)

End point title	Proportion of participants who are alive and free of respiratory failure at Day 28 and Day 60 (participants requiring mechanical ventilation at baseline)
End point description:	
End point type	Secondary
End point timeframe:	
Day 28 and Day 60	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22 ^[14]	59 ^[15]		
Units: Percentage of participants				
number (confidence interval 95%)				
Day 28	54.5 (33.7 to 75.4)	40.7 (28.1 to 53.2)		
Day 60	63.6 (43.5 to 83.7)	47.5 (34.7 to 60.2)		

Notes:

[14] - Analysis population included only participants on mechanical ventilation at baseline

[15] - Analysis population included only participants on mechanical ventilation at baseline

Statistical analyses

Statistical analysis title	Day 60
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-14.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37
upper limit	7.8

Statistical analysis title	Day 28
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.259
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-14.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.4
upper limit	9.2

Secondary: Duration of mechanical ventilation (participants requiring mechanical ventilation at baseline) up to Day 28	
End point title	Duration of mechanical ventilation (participants requiring mechanical ventilation at baseline) up to Day 28
End point description: Participants who die by Day 28 are assigned a duration of 28 days.	
End point type	Secondary
End point timeframe: Up to Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22 ^[16]	59 ^[17]		
Units: Days				
arithmetic mean (confidence interval 95%)	16.7 (11.9 to 21.5)	19.6 (16.8 to 22.4)		

Notes:

[16] - Analysis population included only participants on mechanical ventilation at baseline

[17] - Analysis population included only participants on mechanical ventilation at baseline

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2434
Method	Regression, Linear
Parameter estimate	Difference in means
Point estimate	3.1125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.16
upper limit	8.38

Secondary: Difference in Mortality at Days 14, 28, and 60

End point title	Difference in Mortality at Days 14, 28, and 60
End point description:	
End point type	Secondary
End point timeframe:	
Days 14, 28, and 60	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	430		
Units: Percentage of participants				
number (confidence interval 95%)				

Day 14	9.5 (5.6 to 13.5)	10.0 (7.2 to 12.8)		
Day 28	19.5 (14.2 to 24.9)	18.1 (14.5 to 21.8)		
Day 60	25.7 (19.8 to 31.6)	22.6 (18.6 to 26.5)		

Statistical analyses

Statistical analysis title	Day 14
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8222
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	5.6

Statistical analysis title	Day 28
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6944
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	5.2

Statistical analysis title	Day 60
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population

Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3919
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	4

Secondary: Time to recovery up to Day 28

End point title	Time to recovery up to Day 28
End point description:	
Defined as the time from randomization to the time when an ordinal scale category of 2 (non-ICU hospital ward or "ready for hospital ward" not requiring supplemental oxygen) or better is observed, not followed by ordinal scale category >2 or death. Participants who die are censored at day 28. 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or <= 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death	
End point type	Secondary
End point timeframe:	
Up to Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	430		
Units: Days				
median (confidence interval 95%)	13.0 (10.0 to 15.0)	13.0 (11.0 to 14.0)		

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population

Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6778
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.957
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.18

Secondary: Proportion of participants who are discharged or "ready for discharge" up to Day 28

End point title	Proportion of participants who are discharged or "ready for discharge" up to Day 28
End point description:	Defined as hospital discharge or "Ready for Discharge" not followed by ordinal scale category >1, hospital readmission or death. 1. Discharged (or "ready for discharge" as evidenced by normal temperature and respiratory rate, and stable oxygen saturation on ambient air or <= 2L supplemental oxygen) 2. Non-intensive care unit (ICU) hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy) 7. Death
End point type	Secondary
End point timeframe:	
Up to Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	430		
Units: Percentage of participants				
number (confidence interval 95%)	67.1 (60.8 to 73.5)	66.0 (61.6 to 70.5)		

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population

Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7692
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	6.8

Secondary: Proportion of participants who require initiation of mechanical ventilation post-baseline or die up to Day 28

End point title	Proportion of participants who require initiation of mechanical ventilation post-baseline or die up to Day 28
End point description:	Participants already on mechanical ventilation at baseline are only counted as an event if death occurs.
End point type	Secondary
End point timeframe:	
Up to Day 28	

End point values	Remdesivir + Placebo (RDV+Placebo) - mITT population	Remdesivir + Tocilizumab (RDV+TCZ) - mITT population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	210	430		
Units: Percentage of participants				
number (confidence interval 95%)	29.0 (22.9 to 35.2)	28.6 (24.3 to 32.9)		

Statistical analyses

Statistical analysis title	Analysis
Comparison groups	Remdesivir + Placebo (RDV+Placebo) - mITT population v Remdesivir + Tocilizumab (RDV+TCZ) - mITT population
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9334
Method	Cochran-Mantel-Haenszel
Parameter estimate	Weighted % difference
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	7.2

Other pre-specified: Percentage of Participants with Adverse Events (AEs) Tabulated by Severity

End point title	Percentage of Participants with Adverse Events (AEs) Tabulated by Severity
End point description:	
<p>AEs were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL Grade 4: Life-threatening consequences; urgent intervention indicated Grade 5: Death related to AE Participants are counted at the highest AE grade experienced. Participants that only received RDV and did not receive TCZ/PBO were included in the RDV+PBO arm of the safety population.</p>	
End point type	Other pre-specified
End point timeframe:	
Up to Day 60	

End point values	Remdesivir + Placebo (RDV+Placebo) - safety population	Remdesivir + Tocilizumab (RDV+TCZ) - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	213	429		
Units: Percentage of participants				
number (not applicable)				
Grade 1	9.9	10.5		
Grade 2	21.1	28.2		
Grade 3	10.3	11.2		
Grade 4	4.2	4.9		
Grade 5	25.8	22.6		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of Participants with any Post-Treatment Infection

End point title	Proportion of Participants with any Post-Treatment Infection
End point description:	
<p>Participants that only received RDV and did not receive TCZ/PBO were included in the RDV+PBO arm of the safety population.</p>	

End point type	Other pre-specified
End point timeframe:	
Up to Day 60	

End point values	Remdesivir + Placebo (RDV+Placebo) - safety population	Remdesivir + Tocilizumab (RDV+TCZ) - safety population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	213	429		
Units: Percentage of Participants				
number (not applicable)				
Serious infections	27.7	22.6		
Infections	35.7	33.3		
Opportunistic infections	2.3	1.4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 60 days

Adverse event reporting additional description:

The safety analysis population consisted of all participants who received any amount of study medication (RDV and/or TCZ/PBO). Participants were grouped according to treatment received rather than treatment assigned at randomization. Participants that only received RDV and not TCZ/PBO were included in the RDV+PBO arm of the safety population.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	REMDESIVIR + TOCILIZUMAB
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Reporting group description:

The safety analysis population consisted of all participants who received any amount of study medication (RDV and/or TCZ/PBO). Participants were grouped according to the treatment received rather than by the treatment assigned at randomization. Participants that only received RDV and did not receive TCZ/PBO were included in the RDV+PBO arm of the safety population.

Reporting group title	REMDESIVIR + PLACEBO
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Reporting group description:

The safety analysis population consisted of all participants who received any amount of study medication (RDV and/or TCZ/PBO). Participants were grouped according to the treatment received rather than by the treatment assigned at randomization. Participants that only received RDV and did not receive TCZ/PBO were included in the RDV+PBO arm of the safety population.

Serious adverse events	REMDESIVIR + TOCILIZUMAB	REMDESIVIR + PLACEBO	
Total subjects affected by serious adverse events			
subjects affected / exposed	141 / 429 (32.87%)	76 / 213 (35.68%)	
number of deaths (all causes)	97	55	
number of deaths resulting from adverse events	11	2	
Vascular disorders			
Aortic thrombosis			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			

subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypovolaemic shock			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	4 / 429 (0.93%)	4 / 213 (1.88%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	4 / 429 (0.93%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
General disorders and administration site conditions			
Brain death			

subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Catheter site haemorrhage			
subjects affected / exposed	2 / 429 (0.47%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 429 (0.47%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Hypothermia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 429 (0.47%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (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 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 429 (0.70%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	5 / 429 (1.17%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	3 / 429 (0.70%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	7 / 429 (1.63%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 7	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			

subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 429 (1.17%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood culture positive			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic enzyme increased subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased subjects affected / exposed	1 / 429 (0.23%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Brain herniation subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Atrioventricular block complete subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
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	2 / 429 (0.47%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest subjects affected / exposed	2 / 429 (0.47%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiogenic shock			
subjects affected / exposed	3 / 429 (0.70%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 429 (0.23%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic left ventricular failure			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular dysfunction			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (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	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brain compression			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (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	5 / 429 (1.17%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			

subjects affected / exposed	5 / 429 (1.17%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 429 (0.00%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 429 (0.23%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neurotoxicity			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			

subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normocytic anaemia			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal wall haematoma			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticular perforation			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pneumoperitoneum			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	3 / 429 (0.70%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	21 / 429 (4.90%)	14 / 213 (6.57%)	
occurrences causally related to treatment / all	5 / 21	1 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure			
subjects affected / exposed	5 / 429 (1.17%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 429 (0.23%)	5 / 213 (2.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 429 (0.00%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacterial sepsis			
subjects affected / exposed	2 / 429 (0.47%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	14 / 429 (3.26%)	8 / 213 (3.76%)	
occurrences causally related to treatment / all	0 / 14	0 / 8	
deaths causally related to treatment / all	0 / 14	0 / 8	
COVID-19 pneumonia			
subjects affected / exposed	36 / 429 (8.39%)	27 / 213 (12.68%)	
occurrences causally related to treatment / all	0 / 36	0 / 27	
deaths causally related to treatment / all	0 / 35	0 / 26	
Enterobacter infection			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	21 / 429 (4.90%)	6 / 213 (2.82%)	
occurrences causally related to treatment / all	13 / 22	4 / 6	
deaths causally related to treatment / all	1 / 6	0 / 1	
Pneumonia acinetobacter			
subjects affected / exposed	2 / 429 (0.47%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	5 / 429 (1.17%)	4 / 213 (1.88%)	
occurrences causally related to treatment / all	2 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia klebsiella			
subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sepsis			
subjects affected / exposed	11 / 429 (2.56%)	6 / 213 (2.82%)	
occurrences causally related to treatment / all	6 / 13	2 / 7	
deaths causally related to treatment / all	2 / 5	0 / 2	
Septic shock			
subjects affected / exposed	23 / 429 (5.36%)	10 / 213 (4.69%)	
occurrences causally related to treatment / all	9 / 23	4 / 10	
deaths causally related to treatment / all	4 / 13	1 / 3	
Pulmonary sepsis			
subjects affected / exposed	1 / 429 (0.23%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 429 (0.23%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	0 / 429 (0.00%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 429 (0.23%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 429 (0.93%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	4 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 429 (0.00%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular device infection			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 429 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 429 (0.23%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	REMDESIVIR + TOCILIZUMAB	REMDESIVIR + PLACEBO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 429 (33.57%)	70 / 213 (32.86%)	
Investigations			
Transaminases increased			
subjects affected / exposed	25 / 429 (5.83%)	10 / 213 (4.69%)	
occurrences (all)	25	10	
Vascular disorders			
Hypotension			
subjects affected / exposed	19 / 429 (4.43%)	12 / 213 (5.63%)	
occurrences (all)	19	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 429 (3.03%)	14 / 213 (6.57%)	
occurrences (all)	13	15	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	54 / 429 (12.59%)	25 / 213 (11.74%)	
occurrences (all)	54	25	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed occurrences (all)	24 / 429 (5.59%) 25	11 / 213 (5.16%) 11	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	20 / 429 (4.66%) 21	11 / 213 (5.16%) 11	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	23 / 429 (5.36%) 26	6 / 213 (2.82%) 9	
Hyperglycaemia subjects affected / exposed occurrences (all)	22 / 429 (5.13%) 22	9 / 213 (4.23%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2020	Changed study design to reflect remdesivir as background therapy; amended protocol to include only the presented study arms; updated eligibility criteria
01 July 2020	Clarified eligibility criteria
21 September 2020	Updated primary efficacy endpoint; updated eligibility criteria; increased sample size
10 December 2020	Updated wording of primary endpoint; updated secondary endpoints; updated sample size estimate
22 February 2021	Added secondary endpoints; updated 'time to event' endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported