Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel group, phase 3, multicenter trial investigating the efficacy and safety of C21 as add-on to standard of care in adult subjects with COVID-19.

Summary

EudraCT number	2021-000264-29
Trial protocol	CZ
Global end of trial date	25 April 2022

Results information

Result version number	v1 (current)
This version publication date	23 November 2023
First version publication date	23 November 2023

Trial information

Trial identification

Sponsor protocol code	VP-C21-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04880642
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vicore Pharma AB
Sponsor organisation address	Kornhamnstorg 53, Stockholm, Sweden, SE-111 27
Public contact	Anne-Katrine Cohrt Head of Clinical Operations, Vicore Pharma AB, anne-katrine.cohrt@vicorepharma.com
Scientific contact	Rohit Batta Chief Medical Officer, Vicore Pharma AB, info@vicorepharma.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	13 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2022
Global end of trial reached?	Yes
Global end of trial date	25 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the efficacy of C21 versus placebo as add-on to standard of care on recovery in subjects with COVID-19.

Protection of trial subjects:

None specific.

Background therapy:

All enrolled patients received standard of care (SoC) COVID-19 treatment.

Evidence for comparator: -

Actual start date of recruitment	16 September 2021
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	Czechia: 39
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Philippines: 8
Country: Number of subjects enrolled	Ukraine: 109
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	India: 76
Country: Number of subjects enrolled	South Africa: 5
Worldwide total number of subjects	272
EEA total number of subjects	39

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	195
From 65 to 84 years	74
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

316 subjects signed informed consent and were screened for participation in the trial. Of these, 44 subjects were screening failures and the remaining 272 subjects were randomised to treatment. Of the 272 randomised subjects, 267 subjects actually received treatment.

Period 1

Period 1 title	Randomisation
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of placebo administered twice daily

Arm title	C21 100 mg BID

Arm description: -

Arm type	Experimental
Investigational medicinal product name	C21
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of 100 mg C21 administered twice daily

Number of subjects in period 1	Placebo	C21 100 mg BID
Started	136	136
Completed	133	134
Not completed	3	2
Consent withdrawn by subject	3	2

Period 2	
Period 2 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of placebo administered twice daily

Arm title	C21 100 mg BID

Arm description: -

Arm type	Experimental
Investigational medicinal product name	C21
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

One oral capsule of 100 mg C21 administered twice daily

Number of subjects in period 2	Placebo	C21 100 mg BID
Started	133	134
Completed	118	117
Not completed	18	19
Adverse event, serious fatal	6	5
Consent withdrawn by subject	3	5
Adverse event, non-fatal	3	5
Not randomized/not treated	3	2
Subject decision to stop IMP treatment	1	-
Subject was withdrawn due to Sponsor discretion	1	-
Lost to follow-up	-	1

Protocol deviation	1	1
Joined	3	2
Non-randomized subjects, added to fit with ITI	3	-
Non-randomized subject, added to fit ITI	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	C21 100 mg BID
Reporting group description: -	

Reporting group values	Placebo	C21 100 mg BID	Total
Number of subjects	136	136	272
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	93	102	195
From 65-84 years	40	34	74
85 years and over	3	0	3
Age continuous			
Age at baseline for the ITT analysis set.			
Units: years			
arithmetic mean	56.5	53.5	
full range (min-max)	21 to 91	18 to 79	-
Gender categorical			
Gender for the ITT analysis set.			
Units: Subjects			
Female	63	57	120
Male	73	79	152
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	45	43	88
Black or African American	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	87	90	177
Other	1	3	4
Not reported	1	0	1
Unknown	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	6	6	12
Not Hispanic or Latino	127	127	254
Not Reported	0	0	0
Unknown	3	3	6

Region of enrolment Units: Subjects			
Columbia	0	2	2
United States	4	4	8
Czechia	19	20	39
Philippines	5	3	8
Ukraine	55	54	109
Brazil	5	4	9
South Africa	3	2	5
India	38	38	76
Russia	7	9	16
Height Units: cm			
arithmetic mean	167.6	168.8	
full range (min-max)	149 to 187	145 to 195	-
Weight Units: kg			
arithmetic mean	79.3	81.9	
full range (min-max)	43.0 to 159.0	50.0 to 200.0	-
Body mass index (BMI) Units: kg/m2			
arithmetic mean	28.1	28.7	
full range (min-max)	13.3 to 57.0	19.0 to 69.2	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	C21 100 mg BID
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	C21 100 mg BID
Reporting group description: -	

Primary: All-cause mortality up to Day 60 (ITT)	
End point title	All-cause mortality up to Day 60 (ITT)
End point description:	
End point type	Primary
End point timeframe:	
Day 1 to Day 60	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136[1]	136[2]		
Units: Subjects				
Death	10	10		
Censored	126	126		

Notes:

[1] - ITT analysis set

[2] - ITT analysis set

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	C21 100 mg BID v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.949
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.36

Primary: All-cause mortality up to Day 60 (PP)

End point title	All-cause mortality up to Day 60 (PP)

End point description:

End point type	Primary

End point timeframe:

Day 1 to Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	111		
Units: Subjects				
Death	9	8		
Censored	107	103		

Statistical analyses

Statistical analysis title	Sensitivity analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.948
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.35
upper limit	2.34

Secondary: Time to sustained hospital discharge up to Day 60 (ITT)

End point title	Time to sustained hospital discharge up to Day 60 (ITT)

End point description:

End point type	Secondary
End point timeframe: Day 1 to Day 60	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Days				
median (confidence interval 95%)	9.0 (8.0 to 11.0)	9.0 (7.0 to 11.0)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.52

Secondary: Time to sustained hospital discharge up to Day 60 (PP)

End point title	Time to sustained hospital discharge up to Day 60 (PP)
End point description:	

End point type	Secondary
End point timeframe: Day 1 to Day 60	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	111		
Units: Days				
median (confidence interval 95%)	10.0 (8.0 to 13.0)	9.0 (7.0 to 12.0)		

Statistical analyses

Statistical analysis title	Sensitivity analysis (PP)
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.327
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.55

Secondary: Supplemental oxygen-free Days up to Day 29 (ITT)

End point title	Supplemental oxygen-free Days up to Day 29 (ITT)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1 to Day 29	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	125		
Units: Days				
median (full range (min-max))				
Observed value	24.0 (-1 to 28)	24.0 (-1 to 28)		
Imputed dataset	23.0 (-1 to 28)	23.0 (-1 to 28)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.425 [3]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1

Notes:

[3] - Missing data at a time point were imputed using multiple imputation with a logistic regression model.

Statistical analysis title	Sensitivity analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	251
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.447
Method	ANOVA
Parameter estimate	LS mean
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	2.8
Variability estimate	Standard error of the mean
Dispersion value	1.03

Notes:

[4] - Statistics are based on Imputed Values using multiple imputation with a logistic regression model.

Secondary: Proportion of subjects free of respiratory failure at Day 15 (ITT)	
End point title	Proportion of subjects free of respiratory failure at Day 15 (ITT)
End point description:	
The proportion of subjects free of respiratory failure (responders) at Day 15 was calculated	
End point type	Secondary
End point timeframe:	
Day 15	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Percentage of responders				
number (not applicable)				
Observed values	92.3	90.6		
Imputed values	90.1	88.4		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	C21 100 mg BID v Placebo
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.671
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	6
Variability estimate	Standard error of the mean
Dispersion value	3.91

Notes:

[5] - Statistics are based on imputed values.

Secondary: Proportion of subjects free of respiratory failure at Day 15 (PP)

End point title	Proportion of subjects free of respiratory failure at Day 15 (PP)
End point description:	
The proportion of subjects free of oxygen (responders) at Day 15 was calculated	
End point type	Secondary
End point timeframe:	
Day 15	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	111		
Units: Percentage responders				
number (not applicable)				
Observed value	92.2	91.9		
Imputed value	91.6	92.0		

Statistical analyses

Statistical analysis title	Sensitivity analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.926
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	7.5
Variability estimate	Standard error of the mean
Dispersion value	3.67

Notes:

[6] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Secondary: Proportion of subjects discharged from hospital and free of supplemental oxygen-use at Day 15 (ITT)

End point title	Proportion of subjects discharged from hospital and free of supplemental oxygen-use at Day 15 (ITT)

End point description:

Proportion of Subjects Discharged From the Hospital and Free of Supplemental Oxygen-Use (responders) at Day 15 was calculated

End point type	Secondary

End point timeframe:

Day 15

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Percentage responder				
number (not applicable)				
Observed value	70.0	68.8		
Imputed value	67.9	67.6		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.948
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.4
upper limit	10.6
Variability estimate	Standard error of the mean
Dispersion value	5.62

Notes:

[7] - Statistics were based on imputed values using multiple imputation with a logistic regression model.

Secondary: Proportion of subjects discharged from hospital and free of supplemental oxygen-use at Day 15 (PP)

End point title	Proportion of subjects discharged from hospital and free of supplemental oxygen-use at Day 15 (PP)

End point description:

The proportion of subjects discharged from hospital and free of supplemental oxygen-use (responders) at Day 15 was calculated.

End point type	Secondary

End point timeframe:

Day 15

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	111		
Units: Percentage responder				
number (not applicable)				
Observed value	67.8	67.6		
Imputed value	66.7	68.2		

Statistical analyses

Statistical analysis title	Sensitivity analysis (PP)
Comparison groups	C21 100 mg BID v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.801
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.3
upper limit	13.3
Variability estimate	Standard error of the mean
Dispersion value	6.02

Secondary: Supplemental oxygen-free Days up to Day 29 (PP)	
End point title	Supplemental oxygen-free Days up to Day 29 (PP)
End point description:	
End point type	Secondary
End point timeframe:	
Day 1 to Day 29	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: Days				
median (full range (min-max))				
Observed value	23.0 (-1 to 28)	23.0 (-1 to 28)		
Imputed value	23.0 (-1 to 28)	23.0 (-1 to 28)		

Statistical analyses

Statistical analysis title	Sensitivity analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.273
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	2.1

Notes:

[8] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Secondary: All-cause mortality up to Days 8, 15, 22, and 29 (ITT)

End point title	All-cause mortality up to Days 8, 15, 22, and 29 (ITT)

End point description:

End point type	Secondary

End point timeframe:

Days 8, 15, 22, and 29

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Deaths				
Day 8	7	3		
Day 15	7	7		
Day 22	7	9		
Day 29	8	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects discharged from hospital and free of supplemental oxygen-use, Day 8, Day 22, and Day 29 (ITT)

End point title	Proportion of subjects discharged from hospital and free of supplemental oxygen-use, Day 8, Day 22, and Day 29 (ITT)

End point description:

Summary of proportion of subjects discharged from hospital and free of supplemental oxygen-use by time point using a multiple imputation method

End point type	Secondary

End point timeframe:

Day 8, Day 22 or Day 29

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Percentage responders				
number (not applicable)				
Day 8	36.8	46.8		
Day 22	82.0	80.8		
Day 29	85.1	84.6		

Statistical analyses

Statistical analysis title	Statistical analysis, Day 8
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.075
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	21
Variability estimate	Standard error of the mean
Dispersion value	5.62

Notes:

[9] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 22
Comparison groups	C21 100 mg BID v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.806
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	8.3
Variability estimate	Standard error of the mean
Dispersion value	4.83

Notes:

[10] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 29
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.9
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	8.1
Variability estimate	Standard error of the mean
Dispersion value	4.39

Notes:

[11] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Secondary: Proportion of hospitalized subjects on non-invasive mechanical ventilation, invasive mechanical ventilation, ECMO or using supplemental oxygen, Day 8, Day 15, Day 22, Day 29 and Day 60 (ITT)

End point title	Proportion of hospitalized subjects on non-invasive mechanical ventilation, invasive mechanical ventilation, ECMO or using supplemental oxygen, Day 8, Day 15, Day 22, Day 29 and Day 60 (ITT)

End point description:

End point type	Secondary

End point timeframe:

Day 8, Day 15, Day 22, Day 29 or Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Percentage of responders				
number (not applicable)				
Day 8	33.1	27.8		

Day 15	19.0	14.7		
Day 22	15.5	13.3		
Day 29	14.1	13.2		
Day 60	7.5	7.3		

Statistical analyses

Statistical analysis title	Statistical analysis, Day 8
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.332
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.8
upper limit	5.3
Variability estimate	Standard error of the mean
Dispersion value	5.38

Notes:

[12] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 15

Statistical analysis description:

Proportion of Hospitalized Subjects on Non-Invasive Mechanical Ventilation, Invasive Mechanical Ventilation, ECMO or with Supplemental Oxygen Use by Time Point was calculated using imputed values

Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.348
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	4.7
Variability estimate	Standard error of the mean
Dispersion value	4.64

Notes:

[13] - Statistics are based on imputed values using multiple imputation with a logistic regression model

Statistical analysis title	Statistical analysis, Day 22
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.61
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	6.4
Variability estimate	Standard error of the mean
Dispersion value	4.4

Notes:

[14] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 29
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.843
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	7.5
Variability estimate	Standard error of the mean
Dispersion value	4.23

Notes:

[15] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 60
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.948
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	6
Variability estimate	Standard error of the mean
Dispersion value	3.16

Notes:

[16] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Secondary: Proportion of Subjects Free of Respiratory Failure at Days 8, 22, 29, and 60 (ITT)

End point title	Proportion of Subjects Free of Respiratory Failure at Days 8, 22, 29, and 60 (ITT)

End point description:

Proportion of Subjects Free of Respiratory Failure by Time Point was calculated using a Multiple Imputation Method

End point type	Secondary

End point timeframe:

Day 8, Day 22, Day 29 and Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Percentage responders				
number (not applicable)				
Day 8	91.0	93.2		
Day 22	93.3	93.5		
Day 29	93.3	93.5		
Day 60	92.5	92.7		

Statistical analyses

Statistical analysis title	Statistical analysis, Day 8
Comparison groups	C21 100 mg BID v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.52
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	2.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	8.8
Variability estimate	Standard error of the mean
Dispersion value	3.36

Notes:

[17] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 22
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.95
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	6.1
Variability estimate	Standard error of the mean
Dispersion value	3.01

Notes:

[18] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 29
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.95
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	6.1
Variability estimate	Standard error of the mean
Dispersion value	3.01

Notes:

[19] - Statistics are based on imputed values using multiple imputation with a logistic regression model.

Statistical analysis title	Statistical analysis, Day 60
Comparison groups	Placebo v C21 100 mg BID

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.948
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	6.4
Variability estimate	Standard error of the mean
Dispersion value	3.16

Notes:

[20] - Statistics are based on imputed values using multiple imputation with a logistic regression model

Secondary: Respiratory Failure-Free Days up to Day 60 (ITT)

End point title	Respiratory Failure-Free Days up to Day 60 (ITT)

End point description:

Respiratory Failure-Free Days up to Day 60 are calculated. Missing data at a time point is imputed using multiple imputation with a logistic regression model.

End point type	Secondary

End point timeframe:

Day 1 to Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Days				
median (full range (min-max))	59.0 (0 to 59.0)	59.0 (0 to 59.0)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.881
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Proportion of subjects in each category of the 8-point ordinal scale, Day 8 (ITT)

End point title	Proportion of subjects in each category of the 8-point ordinal scale, Day 8 (ITT)

End point description:

End point type	Secondary

End point timeframe:

Day 8

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	131	129		
Units: Percentage subjects				
number (not applicable)				
Score 1	27.5	38.0		
Score 2	11.5	9.3		
Score 3	9.9	5.4		
Score 4	19.1	18.6		
Score 5	23.7	21.7		
Score 6	2.3	3.9		
Score 7	1.5	0.8		
Score 8	4.6	2.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects in Each Category of the 8-Point Ordinal Scale, Day 15 (ITT)

End point title	Proportion of Subjects in Each Category of the 8-Point Ordinal Scale, Day 15 (ITT)

End point description:

End point type	Secondary

End point timeframe:

Day 15

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	130	128		
Units: Percentage subjects				
number (not applicable)				
Score 1	56.9	59.4		
Score 2	14.6	10.9		
Score 3	3.8	1.6		
Score 4	7.7	15.6		
Score 5	9.2	3.1		
Score 6	1.5	4.7		
Score 7	0.8	0		
Score 8	5.4	4.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects in each category of the 8-point ordinal scale, Day 22 (ITT)

End point title	Proportion of subjects in each category of the 8-point ordinal scale, Day 22 (ITT)

End point description:

End point type	Secondary

End point timeframe:

Day 22

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	127		
Units: Percentage subjects				
number (not applicable)				
Score 1	75.0	78.0		
Score 2	11.7	8.7		
Score 3	0	0.8		
Score 4	2.3	3.9		
Score 5	4.7	1.6		
Score 6	0.8	0		
Score 7	0	0		
Score 8	5.5	7.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects in Each Category of the 8-Point Ordinal Scale, Day 29 (ITT)

End point title	Proportion of Subjects in Each Category of the 8-Point Ordinal Scale, Day 29 (ITT)

End point description:

End point type	Secondary

End point timeframe:

Day 29

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	127		
Units: Percentage subjects				
number (not applicable)				
Score 1	84.4	85.8		
Score 2	6.3	5.5		
Score 3	0	0		
Score 4	0	0.8		
Score 5	2.3	0.8		
Score 6	0.8	0		
Score 7	0	0		
Score 8	6.3	7.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects in Each Category of the 8-Point Ordinal Scale, Day 60 (ITT)

End point title	Proportion of Subjects in Each Category of the 8-Point Ordinal Scale, Day 60 (ITT)

End point description:

End point type	Secondary

End point timeframe:
Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	127		
Units: Percentage subjects				
number (not applicable)				
Score 1	87.5	89.0		
Score 2	4.7	3.1		
Score 3	0	0		
Score 4	0	0		
Score 5	0	0		
Score 6	0	0		
Score 7	0	0		
Score 8	7.8	7.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Needing ICU Stay at Days 8, 15, 22, 29, and 60 (ITT)

End point title	Proportion of Subjects Needing ICU Stay at Days 8, 15, 22, 29, and 60 (ITT)

End point description:

End point type	Secondary

End point timeframe:
Day 8, Day 15, Day 22, Day 29 or Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Percentage responders				
number (not applicable)				
Day 8	12.5	8.1		
Day 15	9.6	8.1		
Day 22	7.4	8.1		
Day 29	8.1	8.1		
Day 60	8.8	8.1		

Statistical analyses

Statistical analysis title	Statistical analysis, Day 8
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.193
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	3.63

Statistical analysis title	Statistical analysis, Day 15
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	5
Variability estimate	Standard error of the mean
Dispersion value	3.42

Statistical analysis title	Statistical analysis, Day 22
Comparison groups	Placebo v C21 100 mg BID

Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.9
upper limit	6.8
Variability estimate	Standard error of the mean
Dispersion value	3.23

Statistical analysis title	Statistical analysis, Day 29
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.935
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	6.2
Variability estimate	Standard error of the mean
Dispersion value	3.3

Statistical analysis title	Statistical analysis, Day 60
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.761
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	5.6

Variability estimate	Standard error of the mean
Dispersion value	3.37

Secondary: Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29, and 60

End point title	Proportion of subjects on invasive mechanical ventilation or ECMO at Days 8, 15, 22, 29, and 60
End point description:	
Missing data at a time point is imputed using multiple imputation with a logistic regression model	
End point type	Secondary
End point timeframe:	
Day 8, Day 15, Day 22, Day 29 or Day 60	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Percentage responders				
number (not applicable)				
Day 8	6.5	3.1		
Day 15	8.3	7.3		
Day 22	6.0	6.5		
Day 29	6.0	6.5		
Day 60	7.5	7.3		

Statistical analyses

Statistical analysis title	Statistical analysis, Day 8
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.213
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	1.9
Variability estimate	Standard error of the mean
Dispersion value	2.7

Statistical analysis title	Statistical analysis, Day 15
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.8
upper limit	5.7
Variability estimate	Standard error of the mean
Dispersion value	3.44

Statistical analysis title	Statistical analysis, Day 22
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.848
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	6.3
Variability estimate	Standard error of the mean
Dispersion value	2.93

Statistical analysis title	Statistical analysis, Day 29
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.848
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	6.3
Variability estimate	Standard error of the mean
Dispersion value	2.93

Statistical analysis title	Statistical analysis, Day 60
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.948
Method	Regression, Logistic
Parameter estimate	Risk difference (RD)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	6
Variability estimate	Standard error of the mean
Dispersion value	3.16

Secondary: Duration of Invasive Mechanical Ventilation/ECMO Use up to Day 60

End point title	Duration of Invasive Mechanical Ventilation/ECMO Use up to Day 60

End point description:

End point type	Secondary

End point timeframe:

Day 1 to Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Days				
median (full range (min-max))	0.0 (0 to 58)	0.0 (0 to 57)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.818
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Duration of hospitalization, incl. re-hospitalization, up to Day 60 (ITT)

End point title	Duration of hospitalization, incl. re-hospitalization, up to Day 60 (ITT)
End point description:	
Missing data at a time point is imputed using multiple imputation with a logistic regression model.	
End point type	Secondary
End point timeframe:	
Day 1 to Day 60	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Days				
median (full range (min-max))	10.0 (2.0 to 60.0)	9.3 (1.0 to 60.0)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.479
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.3

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

Secondary: Duration of ICU stay, incl. re-admission, up to Day 60 (ITT)	
End point title	Duration of ICU stay, incl. re-admission, up to Day 60 (ITT)
End point description:	

End point type	Secondary
End point timeframe:	
Day 1 to Day 60	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Days				
median (full range (min-max))	5.6 (0 to 60)	4.8 (0 to 60)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.419
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Secondary: Change from baseline in SpO2/FiO2 at Day 15 (ITT)	
End point title	Change from baseline in SpO2/FiO2 at Day 15 (ITT)

End point description:

End point type	Secondary

End point timeframe:

Day 15

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	136		
Units: Percentage				
arithmetic mean (full range (min-max))	1.97 (-0.6 to 3.6)	2.06 (-0.7 to 3.6)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.293
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.149
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.129
upper limit	0.427
Variability estimate	Standard error of the mean
Dispersion value	0.141

Notes:

[21] - LS mean, standard error, confidence intervals, and two-sided p-value are from an Analysis of Covariance (ANCOVA).

Secondary: PK parameters - Cmax, C6

End point title	PK parameters - Cmax, C6

End point description:

PK parameters were calculated in the PK population of 7 subjects. Only 6 subjects were included in the calculation of C6.

End point type	Secondary

End point timeframe:

Day 1

End point values	C21 100 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng/ml				
geometric mean (full range (min-max))				
Cmax	981.5 (446 to 3560)			
C6	86.2 (22 to 450)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameters, AUC(0-6), AUC(0-inf), AUClast

End point title	PK Parameters, AUC(0-6), AUC(0-inf), AUClast

End point description:

PK Parameters were calculated in the PK population of 7 subjects. Only 6 subjects were included in the analysis of AUC(0-6) and only 3 subjects were included in the analysis of AUC(0-inf).

End point type	Secondary

End point timeframe:

Day 1

End point values	C21 100 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: h*ng/ml				
geometric mean (full range (min-max))				
AUC(0-6)	2263.8 (1373 to 5625)			
AUC(0-inf)	3000.1 (1537 to 6052)			
AUClast	1902.0 (669 to 5625)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters - tmax

End point title	PK parameters - tmax

End point description:

PK parameters were calculated in the PK population of 7 subjects.

End point type	Secondary

End point timeframe:

Day 1

End point values	C21 100 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours				
median (full range (min-max))	1.0 (1 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in safety laboratory assesments

End point title	Changes in safety laboratory assesments

End point description:

Clinically significant changes from baseline in hematology, clinical chemistry, or urinalysis parameters were monitored and no clinically meaningful mean changes from baseline were observed.

End point type	Secondary

End point timeframe:

Day 1 to Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: Clinically meaningful changes	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Withdrawals due to adverse events

End point title	Withdrawals due to adverse events

End point description:

End point type	Secondary

End point timeframe:

Day 1 to Day 60

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	134		
Units: Subjects/events				
Subjects	9	11		
Events	10	11		

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameters - t1/2

End point title	PK parameters - t1/2

End point description:

PK parameters were calculated in the PK population of 7 subjects. Only 3 subjects were included in the analysis of t1/2.

End point type	Secondary

End point timeframe:

Day 1

End point values	C21 100 mg BID			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Hours				
arithmetic mean (standard deviation)	1.2 (± 0.55)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in CRP at Day 15

End point title	Change from baseline in CRP at Day 15

End point description:

End point type	Other pre-specified

End point timeframe:

Day 15

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	79		
Units: mg/L				
arithmetic mean (standard deviation)	-33.22 (± 53.87)	-20.19 (± 59.031)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	ANCOVA
Parameter estimate	Risk ratio (RR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	2.14

Other pre-specified: Change from baseline in LDH at Day 15

End point title	Change from baseline in LDH at Day 15
End point description:	
End point type	Other pre-specified
End point timeframe:	
Day 15	

End point values	Placebo	C21 100 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	77		
Units: U/L				
arithmetic mean (standard deviation)	-101.72 (± 178.64)	-81.35 (± 185.06)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Placebo v C21 100 mg BID
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.439
Method	ANCOVA
Parameter estimate	Risk ratio (RR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.14

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs were collected from signing of the ICF until Day 29. SAEs were collected until Day 60	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Placebo group
Reporting group description: -	
Reporting group title	C21 group
Reporting group description: -	

Serious adverse events	Placebo group	C21 group	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 133 (9.77%)	15 / 134 (11.19%)	
number of deaths (all causes)	10	10	
number of deaths resulting from adverse events	10	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure acute			

subjects affected / exposed	3 / 133 (2.26%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Frederick's syndrome			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (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			
Death			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 133 (0.75%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Acute respiratory failure			
subjects affected / exposed	1 / 133 (0.75%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary embolism			
subjects affected / exposed	0 / 133 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 133 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (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	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 133 (1.50%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Pneumonia			
subjects affected / exposed	1 / 133 (0.75%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (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			
Hyperkalaemia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	
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: 3 %

Non-serious adverse events	Placebo group	C21 group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 133 (18.05%)	22 / 134 (16.42%)	
Investigations			

Alanine aminotransferase increased subjects affected / exposed occurrences (all)	6 / 133 (4.51%) 6	7 / 134 (5.22%) 9	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 133 (3.76%) 6	4 / 134 (2.99%) 4	
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 4	1 / 134 (0.75%) 1	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 4 6 / 133 (4.51%) 6	4 / 134 (2.99%) 4 4 / 134 (2.99%) 4	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 7	7 / 134 (5.22%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 July 2021	Protocol amendment 2, protocol version 3.0, 2-jul-2021: •Change in LDH was added as an exploratory endpoint • Interim analysis and DMC process was clarified. Ad hoc safety review meeting was added • Description of individual change in ordinal scale scores reflected in the original primary endpoint (see Protocol Version 5.0 below) was added • India-specific age limits and SpO2 criteria added to Inclusion Criteria 1 and 7, respectively. • Active TB was added to Exclusion Criterion 2 • SpO2/FiO2 ratio was added to Exclusion Criterion 9 • Oral dispersion and nasoenteral feeding tube were added as alternative administration forms • List with prohibited medication was added • IMP discontinuation criteria were added for acute kidney and hepatic injury • Text updated to specify that there were no specific criteria for temporary discontinuation of IMP in the protocol • Additional 8-point ordinal scale assessment added at time of hospital discharge and in subjects hospitalized between Days 29 and 60 • Section 8.3 was updated to collect data on all types of hospital re-admissions • Albumin and LDH were added to laboratory parameters • Serum albumin was added to Child-Pugh System table • Plots of cumulative distribution functions were added for the oxygen supplemental free days up to Day 29 endpoint • Additional details on the originally planned interim analysis and sample size re-estimation (See Protocol Version 5.0 below) were provided, including a cap of 450 subjects per treatment group • Option for a third DMC meeting was added • Abstinence was removed from contraceptive and barrier guidance • Procedure for discontinuation of HRT to check menopausal status removed • SoC treatment for COVID-19 was specified • Country specific requirements for India were added
07 December 2021	Protocol amendment 3, Protocol version 4.0, 7-Dec-2021: • Added “hospital-approved diagnostic” PCR test to Inclusion Criterion 2 • Exclusion Criterion 3 rephrased to clarify that the alterations in the Child-Pugh score were to be caused by altered hepatic function, not another underlying disease • Exclusion Criterion 5 changed to a COVID-19 symptom onset >21 days prior to screening (Visit 1) • Oral dispersion was added as an option for subjects with gastric discomfort • Specified that route of administration was captured in the eCRF • Added option of local laboratory analysis of safety samples in special circumstances • Clarification of grading of hepatic impairment (Update of Table 3 in the Protocol [Appendix 16.1.1]) • Subgroup analysis including presence of risk factors for severe COVID-19 was added • Clarified that no adjustment for alpha was required

13 April 2022	This version was submitted and approved in all the countries, except for Colombia where the trial was completed under Protocol Version 4.0. The key changes in Version 5.0 of the protocol included: • The primary endpoint was changed after the last subject was enrolled. The primary endpoint was changed from "proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15" to "all-cause mortality up to Day 60". The previous primary endpoint was then considered a key secondary endpoint. Sections 1.1, 3.0, 4.2, 9.1.1, 9.3.2, and 9.3.3 were updated to reflect these changes. • Sample size was reduced from 600 to 300. Protocol Sections 1.1, 1.2, 4.1, 9.3.1, and 9.5 were updated to reflect the reduced sample size. Power calculations were updated to incorporate the new primary endpoint. •The hierarchy was revised for the statistical comparisons for the primary efficacy endpoint and the key secondary endpoint as follows; all-cause mortality up to Day 60, time to sustained hospital discharge up to Day 60, supplemental oxygen free days up to Day 29, proportion of subjects free of respiratory failure at Day 15, and proportion of subjects discharged from hospital and free of supplemental oxygen at Day 15. This means that statistically significant results for the comparison in the higher rank were required to initiate the testing of the next comparison in the lower rank. Since a step-down procedure was used, each comparison was tested at a significance level of 0.05 and an overall alpha level of 0.05 was preserved. • Removal of the planned interim analysis and sample size re-estimation due to decreased sample size. • Subgroup analyses based on race and ethnicity were added. • The number of subjects for the PK sampling was revised due to the decreased overall sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported