Clinical trial results:
A randomised, double-blind, placebo-controlled, phase 2 trial investigating the safety and efficacy of C21 in hospitalised subjects with COVID-19 infection not requiring mechanical ventilation

Summary

EudraCT number	2020-001502-38
Trial protocol	GB
Global end of trial date	13 October 2020

Results information

Result version number	v1 (current)
This version publication date	30 April 2021
First version publication date	30 April 2021

Trial information

Trial identification

Sponsor protocol code	VP-C21-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04452435
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vicore Pharma AB
Sponsor organisation address	Kronhusgatan 11, Göteborg, Sweden, SE-411 05
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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	18 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2020
Global end of trial reached?	Yes
Global end of trial date	13 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of C21 200 mg daily dose (100 mg b.i.d.) on COVID-19 infection not requiring mechanical ventilation

Protection of trial subjects:

None.

Background therapy:

All subject received standard of care as background therapy.

Evidence for comparator: -

Actual start date of recruitment	27 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	India: 206
Worldwide total number of subjects	206
EEA total number of subjects	0

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)	186
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial planned to enrol 150 subjects. The 106 subjects randomised were all recruited at sites in India. As the number of subjects randomised was considered sufficient to meet the statistical demands of the trial, enrolment was stopped prematurely. This ensured that trial results could be available in a timely manner.

Pre-assignment

Screening details:

206 subjects were enrolled. 96 of the enrolled subjects were screening failures because inclusion criteria 4 (CRP ≥50 and ≤150 mg/L) was not met.
2 enrolled subjects decided to withdraw from the trial before randomisation. 2 subjects died before randomisation (pneumonia). The remaining 106 subjects were randomised to trial treatment

Pre-assignment period milestones

Number of subjects started	206
Number of subjects completed	106

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious fatal: 2
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Screening failure: 96

Period 1

Period 1 title	Overall period (overall period)
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 treatment

Arm description:

Oral placebo treatment twice daily for 7 days

Arm type	Placebo
Investigational medicinal product name	Reference treatment (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg twice daily (BID) for 7 days

Arm title	C21 treatment

Arm description:

Oral C21 treatment of 100 mg twice daily for 7 days

Arm type	Experimental

Investigational medicinal product name	C21
Investigational medicinal product code	
Other name	Compound 21, VP01
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg twice daily (BID) for 7 days

Number of subjects in period 1[1]	Placebo treatment	C21 treatment
Started	55	51
Completed	42	45
Not completed	13	6
Adverse event, serious fatal	3	-
Consent withdrawn by subject	4	1
Discharged from hospital	4	4
Required non-invasive ventilation	1	1
Lost to follow-up	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 206 subjects were enrolled in the trial but only 106 subjects were randomised and were included in the overall or baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo treatment
Reporting group description:	
Oral placebo treatment twice daily for 7 days	
Reporting group title	C21 treatment
Reporting group description:	
Oral C21 treatment of 100 mg twice daily for 7 days	

Reporting group values	Placebo treatment	C21 treatment	Total
Number of subjects	55	51	106
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age at screening			
Units: years			
arithmetic mean	51.1	54.3	
full range (min-max)	22 to 68	29 to 68	-
Gender categorical Units: Subjects			
Female	13	13	26
Male	42	38	80
Supplemental oxygen use at baseline Units: Subjects			
Yes	32	29	61
No	23	22	45
Ethnicity Units: Subjects			
Hispanic or Latino	55	51	106
Not Hispano or Latino	0	0	0
Unknown or Not Reported	0	0	0
Race Units: Subjects			
Asian	55	51	106
CRP value (mg/L) at baseline Units: Subjects			
≤ Median	22	24	46

> Median	25	21	46
Missing	8	6	14

Height			
Height at screening			
Units: cm			
arithmetic mean	166.0	166.1	
full range (min-max)	143 to 188	132 to 198	-
Weight			
Weight at screening			
Units: kg			
arithmetic mean	69.2	70.1	
full range (min-max)	47 to 112	46 to 116	-
BMI			
BMI at screening			
Units: kg/m2			
arithmetic mean	25.1	25.4	
full range (min-max)	20 to 34	15 to 41	-

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) consisted of all subjects who were randomized and received at least 1 dose of IMP and who had at least 1 post-baseline assessment of efficacy.

Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The per-protocol analysis set (PPAS) was a subset of the FAS and consisted of all subjects without any major protocol deviations that were judged to compromise the analysis of the data.

Reporting group values	Full analysis set	Per protocol analysis set	
Number of subjects	106	98	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at screening			
Units: years			
arithmetic mean	52.6	52.8	
full range (min-max)	22 to 68	24 to 68	

Gender categorical Units: Subjects			
Female	26		
Male	80		
Supplemental oxygen use at baseline Units: Subjects			
Yes	61		
No	45		
Ethnicity Units: Subjects			
Hispanic or Latino	0		
Not Hispano or Latino	106		
Unknown or Not Reported	0		
Race Units: Subjects			
Asian	106		
CRP value (mg/L) at baseline Units: Subjects			
≤ Median		46	
> Median		46	
Missing		14	
Height			
Height at screening			
Units: cm			
arithmetic mean	166.1	166.7	
full range (min-max)	132 to 198	132 to 198	
Weight			
Weight at screening			
Units: kg			
arithmetic mean	69.6	70.3	
full range (min-max)	46 to 116	46 to 116	
BMI			
BMI at screening			
Units: kg/m2			
arithmetic mean	25.2	25.3	
full range (min-max)	15 to 41	15 to 41	

End points

End points reporting groups

Reporting group title	Placebo treatment
Reporting group description:	
Oral placebo treatment twice daily for 7 days	
Reporting group title	C21 treatment
Reporting group description:	
Oral C21 treatment of 100 mg twice daily for 7 days	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) consisted of all subjects who were randomized and received at least 1 dose of IMP and who had at least 1 post-baseline assessment of efficacy.	
Subject analysis set title	Per protocol analysis set
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol analysis set (PPAS) was a subset of the FAS and consisted of all subjects without any major protocol deviations that were judged to compromise the analysis of the data.	

Primary: Change From Baseline in C-reactive Protein (CRP) After Treatment With C21 200 mg Daily Dose (100 mg b.i.d.)

End point title	Change From Baseline in C-reactive Protein (CRP) After Treatment With C21 200 mg Daily Dose (100 mg b.i.d.)
End point description:	
Change in C-reactive protein (CRP) from baseline to the average of the last two assessments in the treatment period.	
End point type	Primary
End point timeframe:	
Treatment period of 7 days	

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	45		
Units: mg/L				
least squares mean (confidence interval 90%)	0.22 (0.17 to 0.29)	0.19 (0.14 to 0.25)		

Statistical analyses

Statistical analysis title	Primary endpoint analysis
Comparison groups	Placebo treatment v C21 treatment

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.4891 [2]
Method	ANCOVA

Notes:

[1] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.
[2] - The ratio of adjusted treatment means was 0.85 (90% CI: 0.57, 1.26; p=0.4891), indicating that the null hypothesis could not be rejected.

Statistical analysis title	Subgroup analysis - use of oxygen at baseline

Statistical analysis description:

A subgroup analyses was performed in subjects with supplemental oxygen use at baseline. A total of 26 subjects in the C21 group and 27 in the placebo group were included in the analysis of change in CRP from baseline to the mean of the last 2 non-missing scheduled assessments during the treatment period by baseline supplemental oxygen use.

Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.0881 [4]
Method	ANCOVA

Notes:

[3] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.
[4] - The ratio of adjusted treatment means was 0.59, the 90% CI did not span 1.0 (0.35, 0.98); and the p-value was less than 0.1 (p=0.0881) indicating a statistically significant difference between the groups.

Statistical analysis title	Subgroup analysis - no oxygen use at baseline

Statistical analysis description:

A total of 19 (86.4%) subjects with no supplemental oxygen use at baseline in the C21 group and 19 (82.6%) subjects in the placebo group were included in the analysis of change in CRP by baseline supplemental oxygen use.

Comparison groups	C21 treatment v Placebo treatment
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6285 [5]
Method	ANCOVA

Notes:

[5] - The ratio of adjusted treatment means was 1.20 (90% CI: 0.64, 2.26; p=0.6285), indicating no statistically significant difference between the groups.

Statistical analysis title	Subgroup analysis - age ≤ median

Statistical analysis description:

A total of 20 (87.0%) subjects of median age (54 years) or lower at baseline in the C21 group and 26 (83.9%) in the placebo group were included in the analysis of change in CRP from baseline to the mean of the last 2 non-missing scheduled assessments during the treatment period by baseline age category.

Comparison groups	Placebo treatment v C21 treatment

Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5978 [6]
Method	ANCOVA

Notes:

[6] - The ratio of
adjusted treatment means was 0.85 (90% CI: 0.51, 1.42; p=0.5978), indicating no statistically significant difference between the treatment groups.

Statistical analysis title	Subgroup analysis - age > median

Statistical analysis description:

For subjects above median age (54 years) at baseline, a total of 25 (89.3%) subjects in the C21 group and 20 (83.3%) subjects in the placebo group were included in the analysis of change in CRP by baseline age category.

Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3109 [7]
Method	ANCOVA

Notes:

[7] - The ratio of adjusted
treatment means was 0.70 (90% CI: 0.39, 1.26; p=0.3109), indicating no statistically significant difference between the treatment groups.

Statistical analysis title	Subgroup analysis by sex - women

Statistical analysis description:

A total of 12 (92.3%) women
in the C21 group and 10 (76.9%) women in the placebo group were included in the analysis of change in CRP by sex.

Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0923 [8]
Method	ANCOVA

Notes:

[8] - The ratio of adjusted treatment means
was 0.38, the 90% CI did not span 1.0 (90% CI: 0.14, 0.98) and the p-value was less than 0.1 (p=0.0923), indicating a statistically significant difference between the groups

Statistical analysis title	Subgroup analysis by sex - men

Statistical analysis description:

A total of 33 (86.8%) men in the C21 group and 36 (85.7%) men in the placebo group were included in the analysis of change in CRP from baseline to the mean of the last 2 non-missing scheduled assessments during the treatment period by sex.

Comparison groups	C21 treatment v Placebo treatment
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7134 [9]
Method	ANCOVA

Notes:

[9] - The
ratio of adjusted treatment means was 1.10 (90% CI: 0.71, 1.71; p=0.7134), indicating no statistically significant difference between the treatments.

Statistical analysis title	Subgroup analysis by baseline CRP value ≥ median

Statistical analysis description:

A total of 22 (100.0%) subjects in the C21
group and 24 (100.0%) subjects in the placebo group with median CRP values or higher at baseline were included in the analysis.

Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9374 [10]
Method	ANCOVA

Notes:

[10] - The ratio
of adjusted treatment means was 1.03 (90% CI: 0.58, 1.82; p=0.9374), 0.9374), indicating no statistically significant difference between the treatment groups.

Statistical analysis title	Subgroup analysis by baseline CRP value < median

Statistical analysis description:

A total of 24 (96.0%) subjects with CRP levels lower than median at baseline in the C21 group and 21 (100.0%) in the placebo group were included in the analysis of change in CRP from baseline to the mean of the last 2 non-missing scheduled assessments during the treatment period by baseline CRP category.

Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.22444 [11]
Method	ANCOVA

Notes:

[11] - The ratio in adjusted treatment
means was 0.68 (90% CI: 0.40, 1.15; p=0.2244), indicating no statistically significant difference between the treatment groups.

Secondary: Change from baseline in body temperature

End point title	Change from baseline in body temperature

End point description:

End point type	Secondary

End point timeframe:

Treatment period of 7 days

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	51		
Units: °C				
least squares mean (confidence interval 90%)	-0.34 (-0.47 to -0.21)	-0.11 (-0.25 to 0.02)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - body temperature
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	equivalence[12]
P-value	= 0.0492 [13]
Method	ANCOVA

Notes:

[12] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%

[13] - The difference of 0.23°C in adjusted treatment means between the groups was statistically significant (90% CI: 0.04, 0.42; p=0.0492).

Secondary: Change from baseline in IL-6

End point title	Change from baseline in IL-6

End point description:

End point type	Secondary

End point timeframe:

Treatment period of 7 days

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	31		
Units: pg/mL				
least squares mean (confidence interval 90%)	0.73 (0.51 to 1.03)	0.73 (0.51 to 1.05)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis- IL-6
Comparison groups	Placebo treatment v C21 treatment

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	equivalence[14]
P-value	= 0.9923 [15]
Method	ANCOVA

Notes:

[14] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.
[15] - The ratio of adjusted treatment means was 1.00 (90% CI: 0.61, 1.66; p=0.9923), indicating no statistically significant difference between the treatment groups.

Secondary: Change from baseline in IL-10

End point title	Change from baseline in IL-10

End point description:

Change in IL-10 from baseline to the average of the last two assessments during the treatment period

End point type	Secondary

End point timeframe:

Treatment period of 7 days

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: pg/mL				
least squares mean (confidence interval 90%)	0.73 (0.60 to 0.89)	0.66 (0.54 to 0.80)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - IL-10
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	equivalence[16]
P-value	= 0.5355 [17]
Method	ANCOVA

Notes:

[16] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.
[17] - The ratio of adjusted treatment means was 0.90 (90% CI: 0.68, 1.19; p=0.5355), indicating no statistically significant difference between the treatment groups.

Secondary: Change from baseline in TNF

End point title	Change from baseline in TNF

End point description:

Change in TNF from baseline to the average of the last two assessments during the treatment period.

End point type	Secondary

End point timeframe:

Change in TNF from baseline to the average of the last two assessments during the treatment period.

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: pg/mL				
least squares mean (confidence interval 90%)	1.01 (0.86 to 1.19)	0.91 (0.77 to 1.07)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - TNF
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	equivalence[18]
P-value	= 0.4738 [19]
Method	ANCOVA

Notes:

[18] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.

[19] - The ratio of adjusted treatment means was 0.90 (90% CI: 0.72, 1.14; p=0.4738), indicating no statistically significant difference between the treatment groups.

Secondary: Change from baseline in CA125

End point title	Change from baseline in CA125

End point description:

Change in CA125 from baseline to the average of the last two assessments in the treatment period

End point type	Secondary

End point timeframe:

Treatment period of 7 days

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	46		
Units: u/mL				
least squares mean (confidence interval 90%)	1.16 (1.04 to 1.31)	1.17 (1.05 to 1.31)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - CA125
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence[20]
P-value	= 0.9418 [21]
Method	ANCOVA

Notes:

[20] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.
[21] - The ratio of adjusted treatment means was 0.99 (90% CI: 0.84, 1.17; p=0.9418), indicating no statistically significant difference between the treatment groups.

Secondary: Change from baseline in ferritin

End point title	Change from baseline in ferritin

End point description:

Change in ferritin from baseline to the average of the last two assessments during the treatment period.

End point type	Secondary

End point timeframe:

Treatment period of 7 days

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	46		
Units: ng/mL				
least squares mean (confidence interval 90%)	0.74 (0.66 to 0.84)	0.75 (0.66 to 0.84)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - ferritin
Comparison groups	C21 treatment v Placebo treatment
Number of subjects included in analysis	93
Analysis specification	Pre-specified
Analysis type	equivalence[22]
P-value	= 0.9733 [23]
Method	ANCOVA

Notes:

[22] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.
[23] - The ratio of adjusted treatment means was 1.00 (90% CI: 0.85, 1.19; p=0.9733), indicating no statistically significant difference between the treatment groups.

Secondary: Number of subjects not in need of oxygen supply

End point title	Number of subjects not in need of oxygen supply

End point description:	
Number of subjects not in need of oxygen supply at the end of treatment	
End point type	Secondary
End point timeframe:	
Treatment period of 7 days	

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	51		
Units: Subjects	30	37		

Statistical analyses

Statistical analysis title	Number of subjects not in need of oxygen
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence[24]
P-value	= 0.0568 [25]
Method	Regression, Logistic

Notes:

[24] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%

[25] - The odds ratio for C21 versus placebo was 2.20, the 90% CI did not span 1.0 (90% CI: 1.11, 4.35) and the p-value was less than 0.1 (p=0.0568), showing a statistically significant difference in favour of C21.

Secondary: Number of subjects not in need of mechanical invasive or non-invasive ventilation

End point title	Number of subjects not in need of mechanical invasive or non-invasive ventilation
End point description:	
Number of subjects not in need of mechanical invasive or non-invasive ventilation during the treatment period.	
End point type	Secondary
End point timeframe:	
Treatment period of 7 days	

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	51		
Units: Subjects	53	50		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - ventilation
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence[26]
P-value	= 0.6088 [27]
Method	Regression, Logistic

Notes:

[26] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.

[27] - The odds ratio for 21 versus placebo was 1.89, indicating no statistically significant difference between the treatment groups (90% CI: 0.25, 14.52; p=0.6088.

Secondary: Time to need of mechanical invasive or non-invasive ventilation

End point title	Time to need of mechanical invasive or non-invasive ventilation
End point description:	
Time to need of mechanical invasive or non-invasive ventilation during treatment period.	
End point type	Secondary
End point timeframe:	
Treatment period of 7 days	

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: hours				
arithmetic mean (full range (min-max))	77.925 (59.98 to 95.87)	60.0 (60.0 to 60.0)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - time to ventilation
Comparison groups	Placebo treatment v C21 treatment

Number of subjects included in analysis	3
Analysis specification	Pre-specified
Analysis type	equivalence[28]
P-value	= 0.5757
Method	Logrank

Notes:

[28] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.

Secondary: Time on oxygen supply (for those not needing mechanical invasive or non-invasive ventilation)

End point title	Time on oxygen supply (for those not needing mechanical invasive or non-invasive ventilation)

End point description:

Time on oxygen supply during the treatment period (for those not needing mechanical invasive or non-invasive
ventilation)

End point type	Secondary

End point timeframe:

Treatment period of 7 days

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	51		
Units: Days				
median (inter-quartile range (Q1-Q3))	5.0 (1.0 to 7.0)	5.0 (1.0 to 7.0)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - time on oxygen
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	equivalence[29]
P-value	= 0.8588
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.

Secondary: Adverse Events

End point title	Adverse Events

End point description:

Adverse events were reported from signing of informed consent until end-of-trial visit and are described under adverse events.

End point type	Secondary

End point timeframe:

From signing of informed consent until end-of-trial, 14-17 days

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	51		
Units: Adverse events and subjects	90	64		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Oxygen Supplementation at Day 14

End point title	Oxygen Supplementation at Day 14

End point description:

Number of subjects requiring oxygen supplementation at Day 14

End point type	Post-hoc

End point timeframe:

Follow-up Day 14 (7 days after end-of-treatment)

End point values	Placebo treatment	C21 treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	51		
Units: Subjects	11	1		

Statistical analyses

Statistical analysis title	Post-hoc analysis - Day 14
Comparison groups	Placebo treatment v C21 treatment
Number of subjects included in analysis	106
Analysis specification	Post-hoc
Analysis type	equivalence[30]
P-value	= 0.003 [31]
Method	Chi-squared

Notes:

[30] - The null hypothesis was that the treatments were equivalent and was to be rejected in favour of the alternative hypothesis that a treatment difference existed, if the probability of the null hypothesis being true was less than 10%.

[31] - The post hoc analysis showed that 1 (2.0%) subject in the C21 group and 11 (20.0%) subjects in the placebo group were in need of oxygen supplementation at Day 14, with a statistically significant

difference between the treatment groups (p=0.003).

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From signing of informed consent until end-of-trial visit, 14-19 days.	
Adverse event reporting additional description:	
At each visit, the subject was asked about AEs in an objective manner, e.g., "Have you experienced any problems since the last visit?"	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Placebo treatment
Reporting group description:	
Oral placebo treatment twice daily for 7 days	
Reporting group title	C21 treatment
Reporting group description:	
Oral C21 treatment of 100 mg twice daily for 7 days	

Serious adverse events	Placebo treatment	C21 treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 55 (5.45%)	1 / 51 (1.96%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	3	1	
Cardiac disorders			
Cardio-respiratory arrest			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 55 (1.82%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Infections and infestations			
COVID-19 pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 55 (3.64%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo treatment	C21 treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 55 (65.45%)	30 / 51 (58.82%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 55 (7.27%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Alpha tumour necrosis factor increased			
subjects affected / exposed	3 / 55 (5.45%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 55 (5.45%)	6 / 51 (11.76%)	
occurrences (all)	4	6	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 55 (3.64%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Blood calcium decreased			
subjects affected / exposed	2 / 55 (3.64%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Blood glucose increased			
subjects affected / exposed	3 / 55 (5.45%)	5 / 51 (9.80%)	
occurrences (all)	3	7	
Blood potassium increased			
subjects affected / exposed	2 / 55 (3.64%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Blood urea increased			
subjects affected / exposed	2 / 55 (3.64%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Carbohydrate antigen 125 increased			
subjects affected / exposed	4 / 55 (7.27%)	0 / 51 (0.00%)	
occurrences (all)	4	0	
Interleukin level increased			
subjects affected / exposed	4 / 55 (7.27%)	4 / 51 (7.84%)	
occurrences (all)	4	6	
Lymphocyte count decreased			

subjects affected / exposed	3 / 55 (5.45%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Neutrophil count increased			
subjects affected / exposed	3 / 55 (5.45%)	1 / 51 (1.96%)	
occurrences (all)	5	1	
Platelet count decreased			
subjects affected / exposed	3 / 55 (5.45%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Platelet count increased			
subjects affected / exposed	2 / 55 (3.64%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Serum ferritin increased			
subjects affected / exposed	2 / 55 (3.64%)	5 / 51 (9.80%)	
occurrences (all)	2	5	
White blood cell count increased			
subjects affected / exposed	3 / 55 (5.45%)	0 / 51 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 55 (7.27%)	0 / 51 (0.00%)	
occurrences (all)	4	0	
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	3 / 55 (5.45%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	2 / 55 (3.64%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Hyperglycaemia			
subjects affected / exposed	4 / 55 (7.27%)	11 / 51 (21.57%)	
occurrences (all)	5	14	
Hyponatraemia			
subjects affected / exposed	3 / 55 (5.45%)	2 / 51 (3.92%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2020	The key changes introduced in protocol version 2.0 (14-Aug-2020) were as follows: The planned total number of subjects was increased from 100 to 150 (N=75 in each group) Concomitant medication was allowed to be given according to local SoC (in version 1.0, this had been qualified with 'If considered unlikely to interfere with IMP or the outcome of the trial') The trial was to be conducted at sites globally (version 1.0 was only in the United Kingdom) With the original sample size of 50 subjects per group, there was an approximate 80% power to detect a true CRP reduction of 30 mg/L in C21-treated subjects compared with placebo. With the new sample size of 75 subjects per group, there was an approximate 80% power to detect a true CRP reduction of 25 mg/L in C21-treated subjects compared with placebo

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported