Clinical trial results:
Charité trial of Cenicriviroc (CVC) treatment for COVID-19 patients

Summary

EudraCT number	2020-001493-29
Trial protocol	DE
Global end of trial date	06 January 2022

Results information

Result version number	v1 (current)
This version publication date	22 July 2023
First version publication date	22 July 2023

Trial information

Trial identification

Sponsor protocol code	CVC-for-COVID-19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04500418
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dept. of Hepatology and Gastroenter, Charité - Universitaetsmedizin Berlin, 49 30450 553022, frank.tacke@charite.de
Scientific contact	Dept. of Hepatology and Gastroenter, Charité - Universitaetsmedizin Berlin, 49 30450 553022, frank.tacke@charite.de

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	04 January 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 July 2021
Global end of trial reached?	Yes
Global end of trial date	06 January 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The overall objective of the study is to compare the efficacy of Cenicriviroc (CVC) plus standard of care (SOC) versus SOC alone in participants with COVID-19 with respect to achieving a meaningful response in clinical condition.

Protection of trial subjects:

The trial was conducted in accordance with the declaration of Helsinki and principles of Good Clinical Practice.

Background therapy:

The rationale for CVC use to prevent the "cytokine storm" and respiratory tissue inflammation that results from COVID-19 in infected patients with severe pulmonary dysfunction is based on CVC's ability to block the recruitment of inflammatory CCR2- (monocytes) and CCR5- (lymphocytes) expressing cells to the lung tissue and thus reduce the resulting inflammation-induced tissue damage.

Evidence for comparator: -	
Actual start date of recruitment	20 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	45

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 1 study centers at Charité - Universitätsmedizin Berlin, between 10-Sep-2020 (Date of first enrolment) and 27-Jul-2021 (Date of last completed).

Pre-assignment

Screening details:

A total of 837 subjects entered the screening period, of whom 792 were screening failures.45 subjects were recruited and randomized. Two of them withdrawal after randomization.
Inclusion criteria: adult, SARS-CoV-2-infection confirmed by PCR, 7-point scale score "3" or "4" at enrolment, male or no-pregnant female subjects

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cenicriviroc

Arm description:

Subjects received Cenicriviroc (CVC) plus standard of care

Arm type	Experimental
Investigational medicinal product name	Cenicriviroc mesylate
Investigational medicinal product code	497223-28-6
Other name	Cenicriviroc
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Day 1: 450 milligrams (mg) loading dose of CVC (300mg AM, 150 mg PM) and on Day 2-28: CVC BID 150 mg (AM/PM). Every dose should be taken with food (within 30 min).

Arm title	Placebo

Arm description:

Subjects received placebo plus standard of care ....

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

Dosage and administration details:

Subjects received Day 1: 450 milligrams (mg) Placebo (300mg AM, 150 mg PM) and on Day 2-28: BID PLacebo 150 mg (AM/PM). Every dose should be taken with food (within 30 min).

Number of subjects in period 1[1]	Cenicriviroc	Placebo
Started	27	16
Completed	26	16
Not completed	1	0
Consent withdrawn by subject	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: A total of 38 /42 (90.5%) of the mITT could be followed up for the primary endpoint. Two participants, 1 (placebo) and 1(CVC) withdrew consent after intake of two doses and four doses, and disagreed to further follow up. For two other participants we have been lost contact to one scheduled study visit in time, but continued the study and followed-up with the later study visits.

Baseline characteristics

Reporting groups	
Reporting group title	Cenicriviroc
Reporting group description:	
Subjects received Cenicriviroc (CVC) plus standard of care	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo plus standard of care	

Reporting group values	Cenicriviroc	Placebo	Total
Number of subjects	27	16	43
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 Units: years			
median	57.5	61.5	
inter-quartile range (Q1-Q3)	51.8 to 66.8	50.8 to 68.5	-
Gender categorical Units: Subjects			
Female	7	2	9
Male	20	14	34
Comorbidities Units: Subjects			
BMI >30 kg/m2	14	7	21
Asthma	2	0	2
COPD	4	0	4
NYHA I or II	1	0	1
no cormorbidity	6	9	15
Baseline score on 7-Point ordinal scale			
Subjects responder status defined by the 7-point scale. 1 = not hospitalized, no limitation on activities 2 = not hospitalized, limitation on activities 3 = hospitalized, not requiring supplement oxygen 4 = hospitalized, requiring supplemental oxygen 5 = hospitalized, on non-invasive mechanical ventilation (IMV) or high-flow oxygen devices 6 = hospitalized, on invasive mechanical ventilation (IMV) or Extracorporeal membrane oxygenation (ECMO) 7 = Death			
Units: Subjects			
Score 3	3	3	6

Score 4	22	13	35
Score 5	1	0	1
not recorded	1	0	1
Body mas index (BMI)			
Units: kg/m2			
median	31.4	28.0	
inter-quartile range (Q1-Q3)	26.2 to 33.1	25.9 to 33.3	-
Days from onset to admission			
Units: days			
median	7.1	7.7	
inter-quartile range (Q1-Q3)	4.8 to 9.6	5.8 to 9.8	-
Days from admission to randomization			
Units: Days			
median	1.51	1.21	
inter-quartile range (Q1-Q3)	1.1 to 2	1 to 2	-
Days from symptom onset to randomization			
Units: days			
median	8.7	9.5	
inter-quartile range (Q1-Q3)	6.6 to 10.5	8 to 10.8	-
CRP			
Units: mg/l			
median	88.3	53.3	
inter-quartile range (Q1-Q3)	55.6 to 114.6	36.5 to 74.6	-
PCT			
Units: ng/ml			
median	0.09	0.11	
inter-quartile range (Q1-Q3)	0.01 to 0.1	0.1 to 0.2	-
IL-6			
Units: ng/l			
median	30.2	16.5	
inter-quartile range (Q1-Q3)	18.9 to 54.8	6.8 to 23.4	-
Ferritin			
Units: ng/ml			
median	929.4	1140	
inter-quartile range (Q1-Q3)	532.9 to 1242.6	593.8 to 1776.8	-

End points

End points reporting groups

Reporting group title	Cenicriviroc
Reporting group description: Subjects received Cenicriviroc (CVC) plus standard of care	
Reporting group title	Placebo
Reporting group description: Subjects received placebo plus standard of care	

Primary: Responder outcome Score points " 1 or 2" on 7-point ordinal scale

End point title	Responder outcome Score points " 1 or 2" on 7-point ordinal scale

End point description:

Responder status defined be achieving a "1" or "2" on 7-point ordinal scale- was conducted with binary logistic regression analysis. Responder (yes/no) was included at the outcome variable, treatment group as main effect and strata variables (baseline status 3 vs. 4 or 5 and Comorbidities (yes/no). Due to the small sample size, Firth-Regression was conducted by efficacy analysis. Odds Ratios with 95 % Confidence limits and p- values are reported.
A total of 38 /42 (90.5%) of the mITT could be followed up for the primary endpoint. Two participants, 1 (placebo) and 1 (CVC) withdrew consent after intake of two doses and four doses, and disagreed to further follow up. For two other participants we have been lost contact to one scheduled study visit in time, but continued the study and followed-up with the later study visits.

End point type	Primary

End point timeframe:

day 15 after receiving drug or placebo

End point values	Cenicriviroc	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: subjects				
not recorded	3	1		
Score " 1 or 2" on 7-point ordina	19	14		
no Score "1 or 2"	4	1		

Statistical analyses

Statistical analysis title	CVC vs Placebo
Comparison groups	Cenicriviroc v Placebo

Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	2.24

Statistical analysis title	BL Score category 4 or 5 vs. Score 3
Comparison groups	Cenicriviroc v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.6

Statistical analysis title	comorbidities present vs. not present
Comparison groups	Cenicriviroc v Placebo
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	8.7

Secondary: Score improvement baseline to day 15

End point title	Score improvement baseline to day 15

End point description:

End point type	Secondary

End point timeframe:
from baselinte to day 15

End point values	Cenicriviroc	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: subjects	23	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Oridinal Score day 15

End point title	Oridinal Score day 15

End point description:

End point type	Secondary

End point timeframe:
day 15

End point values	Cenicriviroc	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: subjects				
Score 1	0	2		
Score 2	19	12		
Score 3	2	1		
Score 4	1	0		
Score 5	1	0		
no improvement Score	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Days to improvement of 7-point-Score

End point title	Days to improvement of 7-point-Score

End point description:

End point type	Secondary

End point timeframe:
overall trial

End point values	Cenicriviroc	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: days				
median (inter-quartile range (Q1-Q3))				
Score >= 1	5 (4 to 7)	6 (4 to 7)		
Score >= 2	14 (7 to 22.2)	14 (7 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: NEW Score

End point title	NEW Score

End point description:

End point type	Secondary

End point timeframe:
overall trial

End point values	Cenicriviroc	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: subjects				
NEW score ever <= 2	24	13		
Days until NEW Score <= 2	26	15		

Statistical analyses

No statistical analyses for this end point

Secondary: secondary outcomes

End point title	secondary outcomes

End point description:

End point type	Secondary

End point timeframe:
overall trial

End point values	Cenicriviroc	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: days				
median (inter-quartile range (Q1-Q3))				
Days spent in hospital	6.5 (5 to 8.8)	6 (4 to 7.5)		
Days spent in ICU	0 (0 to 0)	0 (0 to 0)		
IN-hospital days with oxygen	5 (3 to 7)	4 (1 to 5.5)		
exog. oxygen free days in the first 28 d	23 (21 to 25)	24 (22.5 to 27)		

Statistical analyses

No statistical analyses for this end point

Secondary: SARS-CoV-2 PCR results

End point title	SARS-CoV-2 PCR results

End point description:

End point type	Secondary

End point timeframe:
Day 8 and Day 15

End point values	Cenicriviroc	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	16		
Units: subjects				
result "positive d8"	16	5		
result "positive d15"	9	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from vist 1 to visit 11	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups	
Reporting group title	Cenicriviroc (CVC)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Cenicriviroc (CVC)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 27 (37.04%)	1 / 16 (6.25%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Incomplete cardiac systole with short CPR			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke volume			
subjects affected / exposed	0 / 27 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stroke			

subjects affected / exposed	0 / 27 (0.00%)	1 / 16 (6.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ disorder			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia aspiration			

subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Cenicriviroc (CVC)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 27 (92.59%)	13 / 16 (81.25%)	
Investigations			
increased alanine transaminase (ALT/ALAT)			
subjects affected / exposed	14 / 27 (51.85%)	8 / 16 (50.00%)	
occurrences (all)	19	8	
increased aspartate aminotransferase (AST/ASAT)			
subjects affected / exposed	7 / 27 (25.93%)	4 / 16 (25.00%)	
occurrences (all)	7	4	
increased gamma glutamyl transferase (GGT)			
subjects affected / exposed	6 / 27 (22.22%)	1 / 16 (6.25%)	
occurrences (all)	6	1	
increased amylase			
subjects affected / exposed	7 / 27 (25.93%)	3 / 16 (18.75%)	
occurrences (all)	8	3	
increased GOT (glutamic oxalacetic transaminase)			
subjects affected / exposed	3 / 27 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
increased GPT (Glutamat-Pyruvat-Transaminase)			
subjects affected / exposed	5 / 27 (18.52%)	3 / 16 (18.75%)	
occurrences (all)	6	3	
increased alkaline phosphatase			
subjects affected / exposed	3 / 27 (11.11%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
increased lipase			

subjects affected / exposed	7 / 27 (25.93%)	4 / 16 (25.00%)	
occurrences (all)	10	4	
decreased Carbon monoxide diffusing capacity			
subjects affected / exposed	2 / 27 (7.41%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Vital capacity abnormal			
subjects affected / exposed	1 / 27 (3.70%)	2 / 16 (12.50%)	
occurrences (all)	1	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 27 (18.52%)	2 / 16 (12.50%)	
occurrences (all)	6	2	
Cardiac disorders			
Supraventricular extrasystoles			
subjects affected / exposed	0 / 27 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
myocardial repolarisation disorder			
subjects affected / exposed	4 / 27 (14.81%)	0 / 16 (0.00%)	
occurrences (all)	8	0	
Sinus tachycardia			
subjects affected / exposed	3 / 27 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 27 (11.11%)	1 / 16 (6.25%)	
occurrences (all)	3	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 16 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 27 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	3 / 27 (11.11%)	2 / 16 (12.50%)	
occurrences (all)	3	2	
Hypoxia			
subjects affected / exposed	2 / 27 (7.41%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
rash/ exanthema			
subjects affected / exposed	4 / 27 (14.81%)	3 / 16 (18.75%)	
occurrences (all)	5	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2020	update study protocol V.1.2: new - interim safety monitoring, reduced key secondary endpoints, new laboratory parameters, change in inclusion criteria
08 February 2021	update study protocol V.1.3; Changes in safety or integrity of trial subjects Changes in interpretation of scientific documents/value of the trial
09 April 2021	update study protocol V.1.4, Changes in safety or integrity of trial subjects (discontinuation criteria), Changes in interpretation of scientific documents/value of the trial
04 September 2021	update study protocol V.1.5, Changes in safety or integrity of trial subjects, Changes in interpretation of scientific documents/value of the trial

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated before reaching the targeted goal of patients due to persistent recruitment problems despite intensive efforts an due to declining case numbers during spring and summer months. Study recruitment started with a delay.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36572146