Clinical trial results:
Effect of anticoagulation therapy on clinical outcomes in COVID-19 (COVID-PREVENT)

Summary

EudraCT number	2020-002282-33
Trial protocol	DE
Global end of trial date	06 October 2021

Results information

Result version number	v1 (current)
This version publication date	08 June 2023
First version publication date	08 June 2023

Trial information

Trial identification

Sponsor protocol code	COVID-PREVENT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04416048
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - University Hospital of Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Med. Klinik für Kardiologie, Charité - Universitätsmedizin Berlin, +49 30450513702, ulf.landmesser@charite.de
Scientific contact	Prof. Dr. Ulf Landmesser , Charité - CBF, +49 30450513702, ulf.landmesser@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	31 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 June 2021
Global end of trial reached?	Yes
Global end of trial date	06 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of rivaroxaban compared with standard of care (SOC) with the use of prophylactic low molecular weight heparin (LMWH) or unfractionated heparin (UFH) on D-dimer as a clinical marker for the clinical outcome at day 7 post randomization adjusted for baseline measurement in patients with moderate to severe COVID-19.
The co-primary objective is to evaluate the impact of rivaroxaban compared with standard of care (SOC) with the use of prophylactic low molecular weight heparin (LMWH) or unfractionated heparin (UFH) on a seven-category ordinal scale recommended by the WHO as a measure of clinical benefit at day 7 post randomization adjusted for baseline score in patients with moderate to severe COVID-19.

Protection of trial subjects:

Non applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 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	Germany: 111
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	63

From 65 to 84 years	42
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 22 study centers in Germany.

Adults with moderate to severe COVID-19 and a high thrombotic risk were included in the study. Patients with an indication for a chronic anticoagulation or with a high bleeding risk were excluded from the study.

Pre-assignment

Screening details:

A total of 117 patients were screened, 6 were screening failure, so that at the end 111 patients were enrolled and randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban group

Arm description:

Subjects receivedrivaroxaban 20 mg (15 mg for subjects with an eGFR ≥30 mL/min/1.73m2 and <50 mL/min/1.73m2) once daily (OD) for at least 7 days or until hospital discharge, whichever occurred later. After this full-anticoagulation phase, the patients received rivaroxaban 10mg OD for 28 days.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	366789-02-8
Other name	Xarelto
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment with Rivaroxaban 20 mg (15 mg for subjects with an eGFR ≥30 mL/min/1.73m2 and <50 mL/min/1.73m2) once daily (OD) for at least 7 days was given. In case of hospitalization for more than 7 days, the therapeutic treatment with rivaroxaban was continued for the duration of the hospital stay until discharge.

After at least 7 days of therapeutic treatment with rivaroxaban or after hospital discharge, the daily dosage was reduced to 10 mg OD for 28 days.

Arm title	Standard of care

Arm description:

The patients in this group were treated with prophylactic low molecular weight heparin (LMWH) or unfractioned heparin (UFH) until day 7 post randomization or until discharge, whichever occurred later

Arm type	control group
Investigational medicinal product name	Unfractioned heparin of low molecular weight heparin
Investigational medicinal product code	SUB12369MIG
Other name	TINZAPARIN SODIUM
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

The patients in this group were treated with prophylactic low molecular weight heparin (LMWH) or unfractioned heparin (UFH) until day 7 post randomization or until discharge, whichever occurred later.

Number of subjects in period 1	Rivaroxaban group	Standard of care
Started	55	56
Completed	48	48
Not completed	7	8
Adverse event, serious fatal	1	1
Consent withdrawn by subject	4	3
Adverse event, non-fatal	-	1
loss of contact	-	2
Subsequent occurence excl. criteria	1	-
Lost to follow-up	1	-
transfer to another hospital	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban group
Reporting group description:	
Subjects receivedrivaroxaban 20 mg (15 mg for subjects with an eGFR ≥30 mL/min/1.73m2 and <50 mL/min/1.73m2) once daily (OD) for at least 7 days or until hospital discharge, whichever occurred later. After this full-anticoagulation phase, the patients received rivaroxaban 10mg OD for 28 days.	
Reporting group title	Standard of care
Reporting group description:	
The patients in this group were treated with prophylactic low molecular weight heparin (LMWH) or unfractioned heparin (UFH) until day 7 post randomization or until discharge, whichever occurred later	

Reporting group values	Rivaroxaban group	Standard of care	Total
Number of subjects	55	56	111
Age categorical Units: Subjects			
Adults (18-64 years)	31	32	63
From 65-84 years	22	20	42
85 years and over	2	4	6
Gender categorical Units: Subjects			
Female	21	22	43
Male	34	34	68

End points

End points reporting groups

Reporting group title	Rivaroxaban group

Reporting group description:

Subjects receivedrivaroxaban 20 mg (15 mg for subjects with an eGFR ≥30 mL/min/1.73m2 and <50 mL/min/1.73m2) once daily (OD) for at least 7 days or until hospital discharge, whichever occurred later. After this full-anticoagulation phase, the patients received rivaroxaban 10mg OD for 28 days.

Reporting group title	Standard of care

Reporting group description:

The patients in this group were treated with prophylactic low molecular weight heparin (LMWH) or unfractioned heparin (UFH) until day 7 post randomization or until discharge, whichever occurred later

Primary: D-dimer at day 7 post randomization

End point title	D-dimer at day 7 post randomization

End point description:

The primary objective is to assess the effect of rivaroxaban compared with standard of care (SOC) with the use of prophylactic low molecular weight heparin (LMWH) or unfractionated heparin (UFH) on D-dimer as a clinical marker for the clinical outcome at day 7 post randomization adjusted for baseline measurement in patients with moderate to severe COVID-19.
The logarithmic D-dimer measurements (using the natural logarithm) was analyzed by an analysis of covariance (ANCOVA). The model included treatment group and stratification variables of the randomization as factors and the logarithmic baseline D-dimer measurement as covariate. Least squares means for D-dimer at day 7 in the two treatment groups is presented with 95% confidence intervals as well as the difference between the treatment groups at day 7 with 95% confidence interval and p-value testing the null hypothesis of no treatment difference, i.e. a mean difference (on the logarithmic scale) of 0.

End point type	Primary

End point timeframe:

Measurement of D-dimer at day 7 post randomization

End point values	Rivaroxaban group	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	41		
Units: mg/l				
log mean (confidence interval 95%)				
Day 7 post random.	1.21 (0.79 to 1.86)	1.27 (0.79 to 2.04)		

Statistical analyses

Statistical analysis title	treatment effect (log-scale) [log(mg/L)]
Comparison groups	Rivaroxaban group v Standard of care

Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0
Method	ANCOVA
Parameter estimate	mean difference log scale

Primary: Seven-category ordinal scale at day 7 post randomization

End point title	Seven-category ordinal scale at day 7 post randomization

End point description:

Co-primary efficacy outcome:
Regarding the co-primary efficacy outcome, a 7-day course of rivaroxaban at a therapeutic dose of 20 mg daily compared to heparin at a prophylactic dose improved in trend the 7-category ordinal scale as a measure for the clinical outcome.

End point type	Primary

End point timeframe:

7 days post randomization

End point values	Rivaroxaban group	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	54		
Units: number				
Score 1 at Day 7	7	6		
Score 2 at Day 7	19	12		
Score 3 at Day 7	8	13		
Score 4 at Day 7	16	14		
Score 5 at Day 7	3	8		
Score 6 at Day7	1	1		

Statistical analyses

Statistical analysis title	Co-primary efficacy outcome
Comparison groups	Rivaroxaban group v Standard of care
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	rank sum test

Secondary: Secondary efficacy outcome

End point title	Secondary efficacy outcome

End point description:

Time to first event of either of:
- Venous thromboembolism (deep venous thrombosis and/or fatal or non-fatal pulmonary embolism)
- Arterial thromboembolism
- New myocardial infarction
- Non-hemorrhagic stroke
- All-cause death
- Progression to intubation and invasive ventilation

End point type	Secondary

End point timeframe:

Until day 35 post randomization

End point values	Rivaroxaban group	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: days				
Venous thromboembolism	1	4		
Arterial thromboembolism	0	1		
New myocardial infarction	0	2		
Non-hemorrhagic stroke	0	2		
All-cause death	2	1		
Progression to intubation and invasive ventilation	3	2		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Safety outcomes

End point title	Safety outcomes

End point description:

The primary safety outcome occurred in 1 of 111 patients (0.9%) of the whole study population. This patient was assigned to the rivaroxaban group and had a non-fatal major bleeding according to the ISTH criteria.
The secondary efficacy outcome defined as non-major clinical relevant bleeding occurred in two patients in the rivaroxaban-group and in three patients in the SOC-group.

End point type	Other pre-specified

End point timeframe:

overall study

End point values	Rivaroxaban group	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: number				
fatal bleeding	0	0		
non-fatal bleeding (ISTH Criteria)	1	0		
clinically relevant non-major bleeding	2	3		
non-major bleeding (drug interruption >7 d)	1	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events within 24 hours, as well as adverse events that were secondary efficacy endpoints or safety endpoints. Non-serious adverse events were collected and reported in each subsequent visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25

Reporting groups

Reporting group title	Rivaroxaban
Reporting group description: -	
Reporting group title	SOC-Standard or care

Reporting group description: -

Serious adverse events	Rivaroxaban	SOC-Standard or care	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 55 (25.45%)	19 / 56 (33.93%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	1	1	
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 55 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 55 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Ischaemic stroke			

subjects affected / exposed	0 / 55 (0.00%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haematuria	Additional description: Haematuria (since it is a safety endpoint), even when it didn´t fulfill the SAE-Criteria, it was per Protocol a serious adverse event.		
subjects affected / exposed	0 / 55 (0.00%)	3 / 56 (5.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis	Additional description: Epistaxis (since it is a safety endpoint), even when it didn´t fulfill the SAE-Criteria, it was per Protocol a serious adverse event.		
subjects affected / exposed	2 / 55 (3.64%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory insufficiency			
subjects affected / exposed	6 / 55 (10.91%)	6 / 56 (10.71%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 55 (1.82%)	0 / 56 (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			
Superinfection bacterial			
subjects affected / exposed	1 / 55 (1.82%)	2 / 56 (3.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1.5 %

Non-serious adverse events	Rivaroxaban	SOC-Standard or care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 55 (23.64%)	18 / 56 (32.14%)	

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Cardiac disorders			
Myocarditis	Additional description: Suspection of myocarditis due to elevated Troponin T		
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Haematoma			
subjects affected / exposed	2 / 55 (3.64%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 55 (3.64%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Transaminases increased			
subjects affected / exposed	2 / 55 (3.64%)	1 / 56 (1.79%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Exanthema			
subjects affected / exposed	0 / 55 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 55 (3.64%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 55 (3.64%)	2 / 56 (3.57%)	
occurrences (all)	2	2	

Superinfection bacterial			
subjects affected / exposed	0 / 55 (0.00%)	5 / 56 (8.93%)	
occurrences (all)	0	5	
Otitis media			
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Herpes zoster			
subjects affected / exposed	1 / 55 (1.82%)	1 / 56 (1.79%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 55 (0.00%)	2 / 56 (3.57%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2021	The initial planned sample size based on statistical calculations was 400 patients. Due to decreasing COVID incidence rates, it became very likely not to be able to recruit the planned patient number within a reasonable time frame to contribute with the results to the treatment of patients suffering from COVID. The main changes were: - Primary efficacy endpoints and its corresponding statistical analysis - Secondary efficacy endpoints and its corresponding statistical analysis - Sample size determination

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 June 2021	The study was interrupted because of the decreasing numbers of covid patients, to decide to weather continue the trial or to stop it and analyze the available data that was collected until the moment of the interruption.	-

Notes:

Limitations and caveats

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

The biggest limitation of the study was the small number of patients included. Due to the low recruitment, it wasn't possible to test the initial primary hypothesis with the sufficient statistical power. For this reason, the outcomes in the protocol

Notes: