Clinical trial results:
A Randomized, Controlled, Phase 2b Study to Evaluate Safety and Efficacy of Rivaroxaban (Xarelto®) for High Risk People With Mild COVID-19

Summary

EudraCT number	2020-005395-35
Trial protocol	GB
Global end of trial date	29 March 2021

Results information

Result version number	v1
This version publication date	15 October 2021
First version publication date	15 October 2021

Trial information

Trial identification

Sponsor protocol code	Gates MRI - COD-01-T01-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04504032
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bill & Melinda Gates Medical Research Institute
Sponsor organisation address	One Kendall Square, Building 600, Suite 6-301 Cambridge, United States, MA 02139
Public contact	Study Director, Bill & Melinda Gates Medical Research Institute, +1 857 702 2108, clinical.trials@gatesmri.org
Scientific contact	Study Director, Bill & Melinda Gates Medical Research Institute, +1 857 702 2108, clinical.trials@gatesmri.org

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	29 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to assess safety and clinical efficacy of rivaroxaban in people with mild Coronavirus Disease 2019 who are at increased risk of disease progression.

Protection of trial subjects:

The study was conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, and all of the applicable requirements of the United States Code of Federal Regulations (US CFR), 21 CFR Part 50 & 312.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 September 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	United States: 497
Worldwide total number of subjects	497
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)	427
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 538 participants were screened of which only 497 were randomized to treatment.

Period 1

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

Blinding implementation details:

The sponsor had installed a proper firewall to ensure that blinded individuals were insulated from knowledge of unblinded interim results.

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban

Arm description:

Participants self-administered rivaroxaban 10 milligrams (mg) (1 tablet) orally once daily for 21 days.

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

Dosage and administration details:

Participants self-administered rivaroxaban, 10 milligrams (mg) (1 tablet) orally once daily for 21 days.

Arm title	Placebo

Arm description:

Participants self-administered rivaroxaban matching placebo orally once daily for 21 days.

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:

Participants self-administered rivaroxaban matching placebo orally once daily for 21 days.

Number of subjects in period 1	Rivaroxaban	Placebo
Started	246	251
Completed	210	223
Not completed	36	28
Consent withdrawn by subject	9	11
Progressed To Moderate/Severe COVID-19	1	-
Study Terminated By Sponsor	1	2
Adverse event, non-fatal	1	2
Disease Progression Prior To Dosing	15	3
Lost to follow-up	6	9
Drug Supply Issues	1	1
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban
Reporting group description:	
Participants self-administered rivaroxaban 10 milligrams (mg) (1 tablet) orally once daily for 21 days.	
Reporting group title	Placebo
Reporting group description:	
Participants self-administered rivaroxaban matching placebo orally once daily for 21 days.	

Reporting group values	Rivaroxaban	Placebo	Total
Number of subjects	246	251	497
Age categorical Units:			
Age continuous Units: years			
arithmetic mean	49.8	48.6	
standard deviation	± 12.28	± 12.14	-
Gender categorical Units: Subjects			
Female	140	159	299
Male	106	92	198
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	49	46	95
Not Hispanic or Latino	197	201	398
Unknown or Not Reported	0	4	4
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	2	2	4
Asian	0	1	1
Black or African American	17	19	36
Native Hawaiian or Other Pacific Islander	0	0	0
White	219	222	441
Mixed race	0	0	0
Other	7	7	14
Unknown	1	0	1

End points

End points reporting groups

Reporting group title	Rivaroxaban
Reporting group description:	
Participants self-administered rivaroxaban 10 milligrams (mg) (1 tablet) orally once daily for 21 days.	
Reporting group title	Placebo
Reporting group description:	
Participants self-administered rivaroxaban matching placebo orally once daily for 21 days.	

Primary: Number of Participants with Grade 3 and Grade 4 Adverse Events (AEs) through Day 35

End point title	Number of Participants with Grade 3 and Grade 4 Adverse Events (AEs) through Day 35[1]
End point description:	
An AE is any untoward medical occurrence that occurs in a participant. An AE can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with treatment, whether considered related to the product. AEs may include the onset of a new illness or undesirable medical condition or the exacerbation of pre-existing medical conditions. AE severity was graded as Grade 3 (Severe) and Grade 4 (Potentially Life-threatening) per the specific toxicity grading by the Division of Acquired Immunodeficiency Syndrome (DAIDS) AE Grading Table.	
End point type	Primary
End point timeframe:	
Up to Day 35	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this outcome measure.

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	230		
Units: Participants				
number (not applicable)	6	13		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with AEs resulting in study intervention discontinuation through Day 35

End point title	Number of Participants with AEs resulting in study intervention discontinuation through Day 35[2]
End point description:	
An AE is any untoward medical occurrence that occurs in a participant. An AE can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with treatment, whether considered related to the product. AEs may include the onset of new illness or undesirable medical condition or the exacerbation of pre-existing medical conditions.	
End point type	Primary

End point timeframe:

Up to Day 35

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this outcome measure.

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	230		
Units: Participants				
number (not applicable)	4	5		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Serious Adverse Events through Day 35

End point title	Number of Participants with Serious Adverse Events through Day 35[3]

End point description:

A serious AE is any untoward medical occurrence or effect, that, at any dose: results in death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes.

End point type	Primary

End point timeframe:

Up to Day 35

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this outcome measure.

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	219	230		
Units: Participants				
number (not applicable)	2	7		

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants who progressed to moderate or severe disease or higher based on the Gates MRI ordinal scale through Day 28

End point title	Number of participants who progressed to moderate or severe disease or higher based on the Gates MRI ordinal scale through Day 28[4]

End point description:

Participants who progressed to a moderate or severe disease category or higher (Bill & Melinda Gates Medical Research Institute [Gates MRI] ordinal scale ≥3) are reported. Gates MRI scale scores are assessed on a 7-point scale: 1=Asymptomatic/symptoms similar to pre-COVID-19 status; 2=Mild; 3=Moderate or severe; 4=Critically ill; 5=Critically ill with invasive mechanical ventilation or extrapulmonary complication; 6=Critically ill with Extra-Corporeal Membrane Oxygenation (ECMO); 7=Death.

End point type	Primary

End point timeframe:

Up to Day 28

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses was planned for this outcome measure.

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Participants				
number (not applicable)	46	44		

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to disease resolution based on symptoms resolution through Day 28

End point title	Median time to disease resolution based on symptoms resolution through Day 28

End point description:

Time to disease resolution is defined as the time from the first dose to the date of symptoms resolution (new-onset Coronavirus Disease 2019 [COVID-19] symptoms resolved, and pre-existing symptoms returned to Baseline) through Day 28. Baseline refers to health status prior to contracting new-onset COVID-19 symptoms. The 95% confidence interval (CI) for median and quartiles of time to disease resolution were calculated using the Kaplan Meier estimates.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	132	122		
Units: Days				
median (confidence interval 95%)	21.0 (19.0 to 23.0)	23.0 (20.0 to 27.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to disease resolution based on viral clearance and symptoms resolution through Day 28

End point title	Median time to disease resolution based on viral clearance and symptoms resolution through Day 28

End point description:

Time to disease resolution is defined as the time from the first dose to the date of both viral clearance (two consecutive negative diagnostic tests) and symptoms resolution (new-onset COVID-19 symptoms resolved, and pre-existing symptoms returned to Baseline) through Day 28. Baseline refers to health status prior to contracting new-onset COVID-19 symptoms. The 95% CI for median and quartiles of time to disease resolution were calculated using the Kaplan Meier estimates.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	115		
Units: Days				
median (confidence interval 95%)	23.0 (21.0 to 26.0)	26.0 (22.0 to 28.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who progressed to moderate or severe disease or higher based on the Gates MRI ordinal scale at Day 8, 14, and 21

End point title	Number of participants who progressed to moderate or severe disease or higher based on the Gates MRI ordinal scale at Day 8, 14, and 21

End point description:

Participants who progressed to a moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) are reported. Gates MRI ordinal scale scores are assessed on a 7-point scale: 1=Asymptomatic/symptoms similar to pre-COVID-19 status; 2=Mild; 3=Moderate or severe; 4=Critically ill; 5=Critically ill with invasive mechanical ventilation or extrapulmonary complication; 6=Critically ill with ECMO; 7=Death.

End point type	Secondary

End point timeframe:

Days 8, 14, and 21

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Participants				
number (not applicable)				
Day 8	38	36		
Day 14	44	40		
Day 21	45	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved disease resolution based on symptoms resolution at Days 8, 14, 21, and 28

End point title	Number of participants who achieved disease resolution based on symptoms resolution at Days 8, 14, 21, and 28

End point description:

Symptoms resolution is defined as new-onset COVID-19 symptoms resolved, and pre-existing symptoms returned to Baseline. Baseline refers to health status prior to contracting new-onset COVID-19 symptoms.

End point type	Secondary

End point timeframe:

Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Participants				
number (not applicable)				
Day 8	26	30		
Day 14	64	59		
Day 21	100	93		
Day 28	132	122		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who achieved disease resolution based on viral clearance and symptoms resolution at Days 8, 14, 21, and 28

End point title	Number of participants who achieved disease resolution based on viral clearance and symptoms resolution at Days 8, 14, 21, and 28

End point description:

Viral clearance is defined as two consecutive negative diagnostic tests. Symptoms resolution is defined as new-onset COVID-19 symptoms resolved, and pre-existing symptoms returned to Baseline. Baseline refers to health status prior to contracting new-onset COVID-19 symptoms.

End point type	Secondary

End point timeframe:

Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Participants				
number (not applicable)				
Day 8	12	20		
Day 14	49	44		
Day 21	86	83		
Day 28	125	115		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated Gates Medical Research Institute (MRI) scale clinical status at Days 8, 14, 21, and 28

End point title	Number of participants with the indicated Gates Medical Research Institute (MRI) scale clinical status at Days 8, 14, 21, and 28

End point description:

Participants who progressed to a moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) are reported. Gates MRI ordinal scale scores are assessed on a 7-point scale: 1=Asymptomatic/symptoms similar to pre-COVID-19 status; 2=Mild; 3=Moderate or severe; 4=Critically ill; 5=Critically ill with invasive mechanical ventilation or extrapulmonary complication; 6=Critically ill with ECMO; 7=Death.

End point type	Secondary

End point timeframe:

Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Participants				
number (not applicable)				
Day 8: Score 1	33	31		
Day 8: Score 2	152	159		
Day 8: Score 3	3	8		

Day 8: Score 4	0	0		
Day 8: Score 5	0	0		
Day 8: Score 6	0	0		
Day 8: Score 7	0	0		
Day 14: Score 1	69	55		
Day 14: Score 2	114	132		
Day 14: Score 3	3	7		
Day 14: Score 4	0	0		
Day 14: Score 5	0	0		
Day 14: Score 6	0	0		
Day 14: Score 7	0	0		
Day 21: Score 1	98	79		
Day 21: Score 2	87	109		
Day 21: Score 3	1	5		
Day 21: Score 4	0	0		
Day 21: Score 5	0	0		
Day 21: Score 6	0	0		
Day 21: Score 7	0	0		
Day 28: Score 1	125	108		
Day 28: Score 2	57	81		
Day 28: Score 3	1	4		
Day 28: Score 4	0	0		
Day 28: Score 5	0	0		
Day 28: Score 6	0	0		
Day 28: Score 7	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated World Health Organization (WHO) ordinal scale clinical status at Days 8, 14, 21, and 28

End point title	Number of participants with the indicated World Health Organization (WHO) ordinal scale clinical status at Days 8, 14, 21, and 28

End point description:

The WHO ordinal scale score is used to analyze the overall burden of disease and disease severity using an 11-point scale ranging from 0 to 10: 0=Uninfected; No viral ribonucleic acid (RNA) detected; 1=Asymptomatic; viral RNA detected; 2=Symptomatic; independent; 3=Symptomatic; assistance needed; 4=Hospitalized; no oxygen therapy (for isolation only); 5=Hospitalized; oxygen by mask or nasal prongs; 6=Hospitalized; oxygen by non-invasive ventilation (NIV) or high flow; 7=Intubation and mechanical ventilation, partial pressure of oxygen (pO2)/fraction of inspired oxygen (FiO2) ≥150 or oxygen saturation (SpO2)/FiO2 ≥200; 8=Mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2 <200) or Vasopressors; 9=Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO; 10=Dead.

End point type	Secondary

End point timeframe:

Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Participants				
number (not applicable)				
Day 8: Score 0	19	19		
Day 8: Score 1	14	12		
Day 8: Score 2	154	166		
Day 8: Score 3	0	1		
Day 8: Score 4	1	0		
Day 8: Score 5	0	0		
Day 8: Score 6	0	0		
Day 8: Score 7	0	0		
Day 8: Score 8	0	0		
Day 8: Score 9	0	0		
Day 8: Score 10	0	0		
Day 14: Score 0	56	40		
Day 14: Score 1	15	16		
Day 14: Score 2	115	137		
Day 14: Score 3	0	1		
Day 14: Score 4	0	0		
Day 14: Score 5	0	0		
Day 14: Score 6	0	0		
Day 14: Score 7	0	0		
Day 14: Score 8	0	0		
Day 14: Score 9	0	0		
Day 14: Score 10	0	0		
Day 21: Score 0	87	72		
Day 21: Score 1	12	8		
Day 21: Score 2	87	112		
Day 21: Score 3	0	1		
Day 21: Score 4	0	0		
Day 21: Score 5	0	0		
Day 21: Score 6	0	0		
Day 21: Score 7	0	0		
Day 21: Score 8	0	0		
Day 21: Score 9	0	0		
Day 21: Score 10	0	0		
Day 28: Score 0	117	106		
Day 28: Score 1	9	4		
Day 28: Score 2	57	82		
Day 28: Score 3	0	1		
Day 28: Score 4	0	0		
Day 28: Score 5	0	0		
Day 28: Score 6	0	0		
Day 28: Score 7	0	0		
Day 28: Score 8	0	0		
Day 28: Score 9	0	0		
Day 28: Score 10	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with hospitalization through Days 8, 14, 21, and 28

End point title	Number of participants with hospitalization through Days 8, 14, 21, and 28

End point description:

Participants who had clinical worsening and who had at least one hospitalization during the study were analyzed.

End point type	Secondary

End point timeframe:

Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Participants				
number (not applicable)				
Up to Day 8	3	6		
Up to Day 14	3	7		
Up to Day 21	3	7		
Up to Day 28	3	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Median number of days of hospitalization through Day 35

End point title	Median number of days of hospitalization through Day 35

End point description:

Participants who had clinical worsening and who had at least one hospitalization during the study were analyzed. Hospitalized participants without an end date of hospitalization were not included.

End point type	Secondary

End point timeframe:

Up to Day 35

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Days				
median (full range (min-max))	5.0 (4.0 to 5.0)	4.0 (2.0 to 30.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Shift in Gates Medical Research Institute Ordinal Scale Score at Days 8, 14, 21, and 28

End point title	Shift in Gates Medical Research Institute Ordinal Scale Score at Days 8, 14, 21, and 28

End point description:

Gates MRI ordinal scale scores are assessed on a 7-point scale: 1=Asymptomatic/symptoms similar to pre-COVID-19 status; 2=Mild; 3=Moderate or severe; 4=Critically ill; 5=Critically ill with invasive mechanical ventilation or extrapulmonary complication; 6=Critically ill with ECMO; 7=Death. BS= Baseline; PBS= Post-Baseline; NA= Data not available.

End point type	Secondary

End point timeframe:

Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Score on a scale				
number (not applicable)				
Day 8: shift from BS score 1 to PBS score 1	2	1		
Day 8: shift from BS score 1 to PBS score 2	0	0		
Day 8: shift from BS score 1 to PBS score 3	0	0		
Day 8: shift from BS score 1 to PBS score >=4	0	0		
Day 8: shift from BS score 1 to PBS score NA	0	0		
Day 8: shift from BS score 2 to PBS score 1	31	30		
Day 8: shift from BS score 2 to PBS score 2	152	158		
Day 8: shift from BS score 2 to PBS score 3	3	8		
Day 8: shift from BS score 2 to PBS score >=4	0	0		
Day 8: shift from BS score 2 to PBS score NA	7	4		
Day 8: shift from BS score 3 to PBS score 1	0	0		

Day 8: shift from BS score 3 to PBS score 2	0	0		
Day 8: shift from BS score 3 to PBS score 3	0	0		
Day 8: shift from BS score 3 to PBS score >=4	0	0		
Day 8: shift from BS score 3 to PBS score NA	12	3		
Day 8: shift from BS score NA to PBS score 1	0	0		
Day 8: shift from BS score NA to PBS score 2	0	0		
Day 8: shift from BS score NA to PBS score 3	0	0		
Day 8: shift from BS score NA to PBS score >=4	0	0		
Day 8: shift from BS score NA to PBS score NA	15	17		
Day 14: shift from BS score 1 to PBS score 1	2	1		
Day 14: shift from BS score 1 to PBS score 2	0	0		
Day 14: shift from BS score 1 to PBS score 3	0	0		
Day 14: shift from BS score 1 to PBS score >=4	0	0		
Day 14: shift from BS score 1 to PBS score NA	0	0		
Day 14: shift from BS score 2 to PBS score 1	67	54		
Day 14: shift from BS score 2 to PBS score 2	114	131		
Day 14: shift from BS score 2 to PBS score 3	3	7		
Day 14: shift from BS score 2 to PBS score >=4	0	0		
Day 14: shift from BS score 2 to PBS score NA	9	8		
Day 14: shift from BS score 3 to PBS score 1	0	0		
Day 14: shift from BS score 3 to PBS score 2	0	1		
Day 14: shift from BS score 3 to PBS score 3	0	0		
Day 14: shift from BS score 3 to PBS score >=4	0	0		
Day 14: shift from BS score 3 to PBS score NA	12	3		
Day 14: shift from BS score NA to PBS score 1	0	0		
Day 14: shift from BS score NA to PBS score 2	0	0		
Day 14: shift from BS score NA to PBS score 3	0	0		
Day 14: shift from BS score NA to PBS score >=4	0	0		
Day 14: shift from BS score NA to PBS score NA	15	17		
Day 21: shift from BS score 1 to PBS score 1	2	0		
Day 21: shift from BS score 1 to PBS score 2	0	0		

Day 21: shift from BS score 1 to PBS score 3	0	0		
Day 21: shift from BS score 1 to PBS score >=4	0	0		
Day 21: shift from BS score 1 to PBS score NA	0	1		
Day 21: shift from BS score 2 to PBS score 1	96	78		
Day 21: shift from BS score 2 to PBS score 2	87	109		
Day 21: shift from BS score 2 to PBS score 3	1	5		
Day 21: shift from BS score 2 to PBS score >=4	0	0		
Day 21: shift from BS score 2 to PBS score NA	9	8		
Day 21: shift from BS score 3 to PBS score 1	0	1		
Day 21: shift from BS score 3 to PBS score 2	0	0		
Day 21: shift from BS score 3 to PBS score 3	0	0		
Day 21: shift from BS score 3 to PBS score >=4	0	0		
Day 21: shift from BS score 3 to PBS score NA	12	3		
Day 21: shift from BS score NA to PBS score 1	0	0		
Day 21: shift from BS score NA to PBS score 2	0	0		
Day 21: shift from BS score NA to PBS score 3	0	0		
Day 21: shift from BS score NA to PBS score >=4	0	0		
Day 21: shift from BS score NA to PBS score NA	15	17		
Day 28: shift from BS score 1 to PBS score 1	2	1		
Day 28: shift from BS score 1 to PBS score 2	0	0		
Day 28: shift from BS score 1 to PBS score 3	0	0		
Day 28: shift from BS score 1 to PBS score >=4	0	0		
Day 28: shift from BS score 1 to PBS score NA	0	0		
Day 28: shift from BS score 2 to PBS score 1	123	106		
Day 28: shift from BS score 2 to PBS score 2	57	81		
Day 28: shift from BS score 2 to PBS score 3	1	4		
Day 28: shift from BS score 2 to PBS score >=4	0	0		
Day 28: shift from BS score 2 to PBS score NA	12	9		
Day 28: shift from BS score 3 to PBS score 1	0	1		
Day 28: shift from BS score 3 to PBS score 2	0	0		
Day 28: shift from BS score 3 to PBS score 3	0	0		

Day 28: shift from BS score 3 to PBS score >=4	0	0		
Day 28: shift from BS score 3 to PBS score NA	12	3		
Day 28: shift from BS score NA to PBS score 1	0	0		
Day 28: shift from BS score NA to PBS score 2	0	0		
Day 28: shift from BS score NA to PBS score 3	0	0		
Day 28: shift from BS score NA to PBS score >=4	0	0		
Day 28: shift from BS score NA to PBS score NA	15	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Shift in World Health Organization Ordinal Scale Score at Days 8, 14, 21, and 28

End point title	Shift in World Health Organization Ordinal Scale Score at Days 8, 14, 21, and 28

End point description:

The WHO ordinal scale score is used to analyze the overall burden of disease and disease severity using an 11-point scale ranging from 0 to 10: 0=Uninfected; No viral ribonucleic acid (RNA) detected; 1=Asymptomatic; viral RNA detected; 2=Symptomatic; independent; 3=Symptomatic; assistance needed; 4=Hospitalized; no oxygen therapy (for isolation only); 5=Hospitalized; oxygen by mask or nasal prongs; 6=Hospitalized; oxygen by non-invasive ventilation (NIV) or high flow; 7=Intubation and mechanical ventilation, partial pressure of oxygen (pO2)/fraction of inspired oxygen (FiO2) ≥150 or oxygen saturation (SpO2)/FiO2 ≥200; 8=Mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2 <200) or Vasopressors; 9=Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO; 10=Dead. BS= Baseline; PBS= Post-Baseline; NA= Data not available.

End point type	Secondary

End point timeframe:

Baseline; Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	222		
Units: Score on a scale				
number (not applicable)				
Day 8: shift from BS score 0 to PBS score 0	2	0		
Day 8: shift from BS score 0 to PBS score 1	0	0		
Day 8: shift from BS score 0 to PBS score 2	0	0		
Day 8: shift from BS score 0 to PBS score 3	0	0		
Day 8: shift from BS score 0 to PBS score 4	0	0		

Day 8: shift from BS score 0 to PBS score 5	0	0		
Day 8: shift from BS score 0 to PBS score >=6	0	0		
Day 8: shift from BS score 0 to PBS score NA	0	0		
Day 8: shift from BS score 1 to PBS score 0	0	1		
Day 8: shift from BS score 1 to PBS score 1	0	0		
Day 8: shift from BS score 1 to PBS score 2	0	0		
Day 8: shift from BS score 1 to PBS score 3	0	0		
Day 8: shift from BS score 1 to PBS score 4	0	0		
Day 8: shift from BS score 1 to PBS score 5	0	0		
Day 8: shift from BS score 1 to PBS score >=6	0	0		
Day 8: shift from BS score 1 to PBS score NA	0	0		
Day 8: shift from BS score 2 to PBS score 0	17	18		
Day 8: shift from BS score 2 to PBS score 1	14	12		
Day 8: shift from BS score 2 to PBS score 2	154	166		
Day 8: shift from BS score 2 to PBS score 3	0	1		
Day 8: shift from BS score 2 to PBS score 4	1	0		
Day 8: shift from BS score 2 to PBS score 5	0	0		
Day 8: shift from BS score 2 to PBS score >=6	0	0		
Day 8: shift from BS score 2 to PBS score NA	18	7		
Day 8: shift from BS score 3 to PBS score 0	0	0		
Day 8: shift from BS score 3 to PBS score 1	0	0		
Day 8: shift from BS score 3 to PBS score 2	0	0		
Day 8: shift from BS score 3 to PBS score 3	0	0		
Day 8: shift from BS score 3 to PBS score 4	0	0		
Day 8: shift from BS score 3 to PBS score 5	0	0		
Day 8: shift from BS score 3 to PBS score >=6	0	0		
Day 8: shift from BS score 3 to PBS score NA	1	0		
Day 8: shift from BS score NA to PBS score 0	0	0		
Day 8: shift from BS score NA to PBS score 1	0	0		
Day 8: shift from BS score NA to PBS score 2	0	0		
Day 8: shift from BS score NA to PBS score 3	0	0		

Day 8: shift from BS score NA to PBS score 4	0	0		
Day 8: shift from BS score NA to PBS score 5	0	0		
Day 8: shift from BS score NA to PBS score >=6	0	0		
Day 8: shift from BS score NA to PBS score NA	15	17		
Day 14: shift from BS score 0 to PBS score 0	2	0		
Day 14: shift from BS score 0 to PBS score 1	0	0		
Day 14: shift from BS score 0 to PBS score 2	0	0		
Day 14: shift from BS score 0 to PBS score 3	0	0		
Day 14: shift from BS score 0 to PBS score 4	0	0		
Day 14: shift from BS score 0 to PBS score 5	0	0		
Day 14: shift from BS score 0 to PBS score >=6	0	0		
Day 14: shift from BS score 0 to PBS score NA	0	0		
Day 14: shift from BS score 1 to PBS score 0	0	1		
Day 14: shift from BS score 1 to PBS score 1	0	0		
Day 14: shift from BS score 1 to PBS score 2	0	0		
Day 14: shift from BS score 1 to PBS score 3	0	0		
Day 14: shift from BS score 1 to PBS score 4	0	0		
Day 14: shift from BS score 1 to PBS score 5	0	0		
Day 14: shift from BS score 1 to PBS score >=6	0	0		
Day 14: shift from BS score 1 to PBS score NA	0	0		
Day 14: shift from BS score 2 to PBS score 0	54	39		
Day 14: shift from BS score 2 to PBS score 1	15	16		
Day 14: shift from BS score 2 to PBS score 2	115	137		
Day 14: shift from BS score 2 to PBS score 3	0	1		
Day 14: shift from BS score 2 to PBS score 4	0	0		
Day 14: shift from BS score 2 to PBS score 5	0	0		
Day 14: shift from BS score 2 to PBS score >=6	0	0		
Day 14: shift from BS score 2 to PBS score NA	20	11		
Day 14: shift from BS score 3 to PBS score 0	0	0		
Day 14: shift from BS score 3 to PBS score 1	0	0		
Day 14: shift from BS score 3 to PBS score 2	0	0		

Day 14: shift from BS score 3 to PBS score 3	0	0		
Day 14: shift from BS score 3 to PBS score 4	0	0		
Day 14: shift from BS score 3 to PBS score 5	0	0		
Day 14: shift from BS score 3 to PBS score >=6	0	0		
Day 14: shift from BS score 3 to PBS score NA	1	0		
Day 14: shift from BS score NA to PBS score 0	0	0		
Day 14: shift from BS score NA to PBS score 1	0	0		
Day 14: shift from BS score NA to PBS score 2	0	0		
Day 14: shift from BS score NA to PBS score 3	0	0		
Day 14: shift from BS score NA to PBS score 4	0	0		
Day 14: shift from BS score NA to PBS score 5	0	0		
Day 14: shift from BS score NA to PBS score >=6	0	0		
Day 14: shift from BS score NA to PBS score NA	15	17		
Day 21: shift from BS score 0 to PBS score 0	2	0		
Day 21: shift from BS score 0 to PBS score 1	0	0		
Day 21: shift from BS score 0 to PBS score 2	0	0		
Day 21: shift from BS score 0 to PBS score 3	0	0		
Day 21: shift from BS score 0 to PBS score 4	0	0		
Day 21: shift from BS score 0 to PBS score 5	0	0		
Day 21: shift from BS score 0 to PBS score >=6	0	0		
Day 21: shift from BS score 0 to PBS score NA	0	0		
Day 21: shift from BS score 1 to PBS score 0	0	0		
Day 21: shift from BS score 1 to PBS score 1	0	0		
Day 21: shift from BS score 1 to PBS score 2	0	0		
Day 21: shift from BS score 1 to PBS score 3	0	0		
Day 21: shift from BS score 1 to PBS score 4	0	0		
Day 21: shift from BS score 1 to PBS score 5	0	0		
Day 21: shift from BS score 1 to PBS score >=6	0	0		
Day 21: shift from BS score 1 to PBS score NA	0	1		
Day 21: shift from BS score 2 to PBS score 0	85	72		
Day 21: shift from BS score 2 to PBS score 1	12	8		

Day 21: shift from BS score 2 to PBS score 2	87	112		
Day 21: shift from BS score 2 to PBS score 3	0	1		
Day 21: shift from BS score 2 to PBS score 4	0	0		
Day 21: shift from BS score 2 to PBS score 5	0	0		
Day 21: shift from BS score 2 to PBS score >=6	0	0		
Day 21: shift from BS score 2 to PBS score NA	20	11		
Day 21: shift from BS score 3 to PBS score 0	0	0		
Day 21: shift from BS score 3 to PBS score 1	0	0		
Day 21: shift from BS score 3 to PBS score 2	0	0		
Day 21: shift from BS score 3 to PBS score 3	0	0		
Day 21: shift from BS score 3 to PBS score 4	0	0		
Day 21: shift from BS score 3 to PBS score 5	0	0		
Day 21: shift from BS score 3 to PBS score >=6	0	0		
Day 21: shift from BS score 3 to PBS score NA	1	0		
Day 21: shift from BS score NA to PBS score 0	0	0		
Day 21: shift from BS score NA to PBS score 1	0	0		
Day 21: shift from BS score NA to PBS score 2	0	0		
Day 21: shift from BS score NA to PBS score 3	0	0		
Day 21: shift from BS score NA to PBS score 4	0	0		
Day 21: shift from BS score NA to PBS score 5	0	0		
Day 21: shift from BS score NA to PBS score >=6	0	0		
Day 21: shift from BS score NA to PBS score NA	15	17		
Day 28: shift from BS score 0 to PBS score 0	2	0		
Day 28: shift from BS score 0 to PBS score 1	0	0		
Day 28: shift from BS score 0 to PBS score 2	0	0		
Day 28: shift from BS score 0 to PBS score 3	0	0		
Day 28: shift from BS score 0 to PBS score 4	0	0		
Day 28: shift from BS score 0 to PBS score 5	0	0		
Day 28: shift from BS score 0 to PBS score >=6	0	0		
Day 28: shift from BS score 0 to PBS score NA	0	0		
Day 28: shift from BS score 1 to PBS score 0	0	1		

Day 28: shift from BS score 1 to PBS score 1	0	0		
Day 28: shift from BS score 1 to PBS score 2	0	0		
Day 28: shift from BS score 1 to PBS score 3	0	0		
Day 28: shift from BS score 1 to PBS score 4	0	0		
Day 28: shift from BS score 1 to PBS score 5	0	0		
Day 28: shift from BS score 1 to PBS score >=6	0	0		
Day 28: shift from BS score 1 to PBS score NA	0	0		
Day 28: shift from BS score 2 to PBS score 0	115	105		
Day 28: shift from BS score 2 to PBS score 1	9	4		
Day 28: shift from BS score 2 to PBS score 2	57	82		
Day 28: shift from BS score 2 to PBS score 3	0	1		
Day 28: shift from BS score 2 to PBS score 4	0	0		
Day 28: shift from BS score 2 to PBS score 5	0	0		
Day 28: shift from BS score 2 to PBS score >=6	0	0		
Day 28: shift from BS score 2 to PBS score NA	23	12		
Day 28: shift from BS score 3 to PBS score 0	0	0		
Day 28: shift from BS score 3 to PBS score 1	0	0		
Day 28: shift from BS score 3 to PBS score 2	0	0		
Day 28: shift from BS score 3 to PBS score 3	0	0		
Day 28: shift from BS score 3 to PBS score 4	0	0		
Day 28: shift from BS score 3 to PBS score 5	0	0		
Day 28: shift from BS score 3 to PBS score >=6	0	0		
Day 28: shift from BS score 3 to PBS score NA	1	0		
Day 28: shift from BS score NA to PBS score 0	0	0		
Day 28: shift from BS score NA to PBS score 1	0	0		
Day 28: shift from BS score NA to PBS score 2	0	0		
Day 28: shift from BS score NA to PBS score 3	0	0		
Day 28: shift from BS score NA to PBS score 4	0	0		
Day 28: shift from BS score NA to PBS score 5	0	0		
Day 28: shift from BS score NA to PBS score >=6	0	0		
Day 28: shift from BS score NA to PBS score NA	15	17		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Gates Medical Research Institute Ordinal Scale Score at Days 8, 14, 21, and 28

End point title	Change From Baseline in Gates Medical Research Institute Ordinal Scale Score at Days 8, 14, 21, and 28

End point description:

Gates MRI ordinal scale scores are assessed on a 7-point scale: 1=Asymptomatic/symptoms similar to pre- COVID-19 status; 2=Mild; 3=Moderate or severe; 4=Critically ill; 5=Critically ill with invasive mechanical ventilation or extrapulmonary complication; 6=Critically ill with ECMO; 7=Death. Instead of change from baseline, shift in scores from baseline was measured and have been presented in outcome measure 14.

End point type	Other pre-specified

End point timeframe:

Baseline; Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:

[5] - No subjects were analyzed

[6] - No subjects were analyzed

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in World Health Organization Ordinal Scale Score at Days 8, 14, 21, and 28

End point title	Change From Baseline in World Health Organization Ordinal Scale Score at Days 8, 14, 21, and 28

End point description:

The WHO ordinal scale score is used to analyze the overall burden of disease and disease severity using an 11-point scale ranging from 0 to 10: 0=Uninfected; No viral ribonucleic acid (RNA) detected; 1=Asymptomatic; viral RNA detected; 2=Symptomatic; independent; 3=Symptomatic; assistance needed; 4=Hospitalized; no oxygen therapy (for isolation only); 5=Hospitalized; oxygen by mask or nasal prongs; 6=Hospitalized; oxygen by non-invasive ventilation (NIV) or high flow; 7=Intubation and mechanical ventilation, partial pressure of oxygen (pO2)/fraction of inspired oxygen (FiO2) ≥150 or oxygen saturation (SpO2)/FiO2 ≥200; 8=Mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2 <200) or Vasopressors; 9=Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO; 10=Dead. Instead of change from baseline, shift in scores from baseline was measured and have been presented in outcome measure 16.

End point type	Other pre-specified

End point timeframe:
Baseline; Days 8, 14, 21, and 28

End point values	Rivaroxaban	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Score on a scale				
arithmetic mean (standard deviation)	()	()		

Notes:
[7] - No subjects were analyzed
[8] - No subjects were analyzed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of consent up to 14 days after the last dose of study treatment (Day 35).

Adverse event reporting additional description:

Analysis was performed in the Safety Population, comprised of all participants randomly assigned to study intervention, who received the study intervention. Participants were grouped according to the study intervention they actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Rivaroxaban

Reporting group description:

Participants self-administered rivaroxaban 10 milligrams (mg) (1 tablet) orally once daily for 21 days.

Reporting group title	Placebo

Reporting group description:

Participants self-administered rivaroxaban matching placebo orally once daily for 21 days.

Serious adverse events	Rivaroxaban	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 219 (0.91%)	7 / 230 (3.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute kidney injury			
subjects affected / exposed	0 / 219 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			

subjects affected / exposed	0 / 219 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 230 (0.43%)	
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 pneumonia			
subjects affected / exposed	2 / 219 (0.91%)	4 / 230 (1.74%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Rivaroxaban	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 219 (5.48%)	11 / 230 (4.78%)	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 219 (1.37%)	4 / 230 (1.74%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 219 (0.46%)	3 / 230 (1.30%)	
occurrences (all)	1	3	
Renal and urinary disorders			
Hematuria			
subjects affected / exposed	3 / 219 (1.37%)	0 / 230 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	4 / 219 (1.83%)	0 / 230 (0.00%)	
occurrences (all)	4	0	
COVID -19/COVID-19 pneumonia/pneumonia			

subjects affected / exposed occurrences (all)	1 / 219 (0.46%) 1	5 / 230 (2.17%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 September 2020	By means of Amendment 1, emergent and important issues at clinical sites pertaining to screening and enrollment were addressed. These included: (1) the requirement for screening to occur within 72 hours of symptom onset resulted in many potential subjects who had symptoms onset before 72 hours being excluded from consideration for enrollment; and (2) the requirement for Day 1 to occur no later than 72 hours after screening did not take into account the time required to obtain SARS-CoV-2 test results (for subjects not having documentation of a prior positive test) nor the time needed to provide study materials to subjects once randomization had occurred. The time constraints described above restricted enrollment and the study team decided that both constraints needed to be relaxed to enable efficient enrollment. Amendment 1 implemented the changes that subjects had to have documented positive SARS-CoV-2 diagnostic testing with a sample collected ≤ 10 days before screening and had to be symptomatic for COVID-19 for ≤ 7 days at time of randomization. It also implemented that screening procedures had to occur ≤ 5 days prior to the Day 1 visit. Because the putative effect of rivaroxaban to prevent thrombotic complications of COVID-19 would be present during the whole of the treatment period, the expansion of the intervals as detailed above were not anticipated to significantly impact the results of the study.
27 January 2021	By means of Amendment 2, the protocol was amended to reduce the number of interim analyses from 3 to 1 and to remove the sample size re-estimation procedure. Additional changes included modifying the first interim analysis from an evaluation of futility and efficacy to be limited to futility, and to remove any additional pre-specified interim analyses. These changes were made since the pace and trajectory of study enrollment suggested that the targeted number of total study subjects (600) would be met by the time of the proposed data cut for the second planned interim analysis, and that the majority of study subjects would have completed the study by the time of the planned IDMC meeting. Therefore, any decision stemming from the proposed second interim analysis would have been unlikely to affect the study conduct.

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.

Based on Data Monitoring Committee's recommendation on February 3, 2021, the study was stopped due to futility.

Notes: