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Statistical Analysis Plan: Gates MRI-COD-01-T01-01

Study Title:	A Randomized, controlled, Phase 2b study to evaluate safety and efficacy of rivaroxaban (Xarelto®) for high risk people with mild COVID-19
Study Number:	Gates MRI-COD-01-T01-01
Study Phase:	2b
Sponsor:	Bill & Melinda Gates Medical Research Institute (Gates MRI) One Kendall Square Building 600, Suite 6-301 Cambridge, MA 02139
Version	2.0
NCT #:	NCT04504032
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Confidentiality Statement

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2. SIGNATURE PAGE

Study Title: A randomized, controlled, Phase 2b study to evaluate safety and efficacy of rivaroxaban (Xarelto®) for high risk people with mild COVID-19

Protocol Number: Gates MRI - COD-01-T01-01

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
ANOVA	analysis of variance
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
CMH	Cochran-Mantel-Haezszel
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
Ct	Cycle threshold
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
Gates MRI	Bill & Melinda Gates Medical Research Institute
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IP	investigational product
ITT	intention to treat
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention to treat
PCR	polymerase chain reaction
PI	principal investigator
PO	orally
PP	per protocol
PT	preferred term
SAE	serious adverse event

SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SE	standard error
SoA	schedule of activities
SOC	system organ class
WHO	World Health Organization

4. INTRODUCTION

The purpose of this statistical analysis plan is to describe the framework for the reporting, summarization and statistical analysis methodology of the safety and efficacy parameters measured for the Gates Medical Research Institute (MRI) study COD-01-T01-01. It is based on Protocol Gates MRI - COD-01-T01-01 Version 4, Amendment 2, 27 January 2021. This study is performed as part of an adaptive, randomized platform core protocol for treatment of early and mildly symptomatic individuals in out-patient settings with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Additional statistical analysis plans will be developed for future protocols and interventions that will be added to the core protocol.

On January 28 and February 3, 2021, the Independent Data Monitoring Committee (IDMC) met to review the available safety and efficacy data to (1) perform the monthly safety review of accumulating data; and (2) evaluate the results of the first prespecified interim analysis for futility. Based on the review of the data, the IDMC determined on February 3, 2021, that the futility boundary was crossed and recommended that the clinical study be stopped. The final statistical analysis plan was amended to reflect changes to the planned analysis following early termination of the study.

As of February 4, 2021, the following changes were made in the study conduct:

- all randomization is ceased and no new study participants are enrolled.
- current participants must discontinue dosing of all study drug and discard their study drug.
- participants should remain in active, masked follow up and continue their study visits until Day 35 if they have had at least one dose of study drug.
    - Participants who have not reached Day 21 will continue safety follow up only until Day 35. These participants will be monitored for AEs, bleeding events and concomitant medication. These participants will not have further assessments for Gates MRI and WHO ordinal scale, symptoms, and nasal swabs for polymerase chain reaction (PCR) test.
    - Participants who have reached Day 21 but not Day 35 of study will continue safety and efficacy follow up until Day 35. These participants will be monitored for AEs, bleeding events, concomitant medication, Gates MRI and WHO ordinal scales, and symptoms. These participants will not have further nasal swabs for PCR test.
- participants who have not yet taken any study drug will discontinue the study early.

To address potential for substantial under-estimation of the treatment effect, efficacy analyses will be performed on a final efficacy analysis population as described in Section 7.1. Safety analyses will be performed on the Safety analysis population.

5 TRIAL OBJECTIVES

The following objectives and associated endpoints are part of this study.

Table 1: Study objectives and associated endpoints.

Objectives	Endpoints
Primary	
To characterize safety of study intervention	Through Day 35 • Frequencies of grade 3 adverse events (AEs) and grade 4 AEs • AEs resulting in study intervention discontinuation • All SAEs
To assess efficacy of study intervention	• Proportion of participants who progress to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) through Day 28
Secondary	
To assess clinical efficacy of study intervention	• Time to disease resolution, defined as symptoms resolution only (new onset COVID-19 symptoms resolved, and pre-existing symptoms returned to baseline*) through Day 28 • Time to disease resolution, defined as 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. • Proportion of participants who progress to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) at Days 8, 14 and 21 • Proportion of participants who achieve disease resolution, defined as symptoms resolution only, at Days 8, 14, 21 and 28 • Proportion of participants who achieve disease resolution, defined as both viral clearance and symptoms resolution, at Days 8, 14, 21 and 28 • Gates MRI scale score at Days 8, 14, 21 and 28 • World Health Organization (WHO) ordinal scale score at Days 8, 14, 21 and 28 • Incidence and number of days of hospitalization at Days 8, 14, 21 and 28
Exploratory	
To assess virological efficacy	• Quantity (and change from baseline) of SARS CoV-2 virus at Days 8, 14, 21 and 28
To assess viral sequence	• Phylogenetic relationships of SARS-CoV-2 viruses sequenced from positive nasal swab samples

*Baseline refers to health status prior to contracting new onset COVID-19 symptoms.

6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is an adaptive, randomized platform trial for treatment of early and mildly symptomatic individuals in out-patient settings with SARS-CoV-2 infection. The protocol will enroll people at high risk for COVID-19 progression based on age, BMI and comorbidity. The primary outcome through 28 days after the first intervention dose is focused on safety and efficacy (time to disease resolution or progression of disease).

Primary purpose: To assess the safety and clinical efficacy of a rivaroxaban with a primary endpoint of reduction in proportion of participants who progress to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) through Day 28.

Interventional model*:* Participants will be randomized 1:1 to either the rivaroxaban or the placebo group, in parallel for the duration of the study. Randomization will be stratified by site and by number of days since onset of symptoms at time of randomization.

Intervention groups:

Study intervention group: rivaroxaban, 10 mg (1 tablet) orally daily for 21 days.

Control group: placebo-equivalent (multi-vitamin supplement) 1 tablet orally daily for 21 days

Masking: Every effort will be made to mask the assigned treatment groups. Participants and study staff evaluating them will not be told of the assigned treatment groups. The laboratories performing the SARS-CoV-2 diagnostic testing will be blinded. Sponsor will be blinded throughout the study conduct.

Study visits: Every effort will be made to conduct the study protocol visits virtually with the study participants. A web-based video conferencing tool will be employed to allow for virtual (remote) interactions to take place between the study staff and the participant, for screening and all study visits.

Safety and efficacy monitoring: An Independent Data Monitoring Committee (IDMC) will be convened for this study for safety and efficacy monitoring with expertise in COVID-19 or respiratory viruses and emerging epidemics as well as biostatistics.

Changes in randomization strata: The protocol required an amendment after study start to address emergent and important issues at sites pertaining to screening and enrollment. The protocol amendment 1 modified the stratification factor of number of days since onset of symptoms at time of randomization by changing from <3 days vs. ≥3 days to <6 days vs. ≥6 days. Eight participants (1.3%) out of the total planned 600 participants randomized were enrolled under original protocol Gates MRI-COD-01-T01-01 Version 4 dated 01 August 2020 (randomized strata: <3 days vs. ≥3 days). Combining data from the original protocol and amendment 1 for the pre-specified analyses preserves the double-blind nature of the treatment comparison contrast in the same way a patient-level meta-analysis does. Because participants were randomly assigned under both protocols, one can expect participants within each treatment arm to be comparable at baseline under each of the original and amendment 1 protocols. Analyses where participants are analyzed according to the stratum to which they were randomized under the original protocol or protocol amendment 1 are statistically the most appropriate (resulting in 4 total stratification levels); however, the number of participants randomized under the original protocol (randomized strata: <3 days vs. ≥3 days) is relatively very small [8 (1.3%) out of the total planned 600 participants]. Further, since the number of participants randomized to the ≥3 days stratum is extremely small (2 participants) statistical modelling using a randomization factor with 4 stratification levels may not be possible. Because of this, and the fact that it is unlikely that knowledge of the protocol version will meaningfully impact investigators and participants e.g., with respect to participant management, follow-up or endpoint reporting, it is proposed that participants randomized under the original protocol are mapped under the new strata <6 days vs. ≥6 days and analyzed accordingly. Specifically, the 6

participants that were randomized to the <3 days strata will be assigned to the <6 days stratum and the 2 participants that were randomized to the ≥3 days stratum will be assigned to the <6 days vs ≥6 days according to the actual number of days since symptom onset at the time of randomization. As participants are not concurrently recruited for the two versions of the protocol and assignment to protocol version was not at random, analyses will be performed and reported separately for the original and amendment 1 protocols when possible to assess the similarity of the results.

6.2 Efficacy Measures

Efficacy measures include the following:

- Clinical status assessment using ordinal scale for Gates MRI
- COVID-19 symptoms
- Nasal sampling for SARS-Cov-2 diagnostic testing
- Clinical status assessment using ordinal scale for WHO

6.3 Safety Measures

Safety measures include AEs assessment, bleeding events and severity assessment.

7 STUDY POPULATIONS

7.1 Analysis Populations

An interim analysis was conducted on 28 January, 2021 using the data cut of 8 January, 2021. Efficacy interim analyses were produced based on the first 200 randomized participants who either had discontinued the study or had completed Day 28 in the ITT population. The interim efficacy primary endpoint result will be reported in the CSR using the data cut of 8 January, 2021.

IDMC's recommendation that the clinical study be stopped impacts the efficacy evaluation for the participants who were continuing in the study and had not yet reached Day 21 of the study (end of treatment period) as of 4 February, 2021. In order to have meaningful results of the final efficacy analyses, efficacy analyses will be performed on a final efficacy analysis set of participants who met either one the following criteria:

- Completed or discontinued the study or progressed prior to 5 February, 2021.
- Completed Day 21 or later visits as of 5 February, 2021.

Final analysis will be conducted following database lock.

- Efficacy analyses will be produced for randomized participants who meet the selection criteria described above and also meet the analysis population criteria described below.
- Safety analyses will be produced for all participants in the database who received at least one dose of study intervention.

Table 2: Analysis populations

Population	Description
ITT Population	All participants in the ITT population who met the criteria stated above. Participants will be analyzed according to the intervention to which they were randomized.
mITT population	All participants in the ITT population, who received the study interventiona and have mild disease at study entry. Participants will be analyzed according to the intervention they actually received.
PP population	All participants in the ITT population, who received the study interventions as planned, have mild disease at study entry, and did not substantially deviate from the protocol procedures. Participants will be analyzed according to the intervention they actually received.
Safety population	All participants randomly assigned to study intervention, who received the study intervention. Participants will be analyzed according to the intervention they actually received.

7.2 Assigning Shared Controls across Multiple Intervention-specific Analysis Populations

Each intervention may be initiated and stopped at different time frames, and within different sites. Depending on the number of interventions that a participant can be eligible to receive, a participant randomized to a control arm may be part of multiple intervention-specific analysis populations for the purposes of comparing a single intervention to control. We note the following core principles associated with sharing controls across intervention-specific analysis populations:

- Controls will only be shared across multiple intervention-specific populations when there is randomization across those interventions and the control. All participants will only be randomized once.
- A participant who is eligible for multiple interventions at a site will be randomized equally to receive 1 of the interventions for which they are eligible vs control. Participants randomized to control will be equally likely to receive the matched control of each intervention for which they are eligible. If the participant is randomized to control, they will be assigned to each of the intervention-specific analysis populations included in the randomization. A participant randomized to control will not be assigned to an intervention-specific analysis population that was not included in the randomization.
- Controls will only be shared contemporaneously. A participant can only be used in the intervention-specific population(s) that was available and included at the time of their randomization.
- A control does not have to receive the intervention-specific matched control to be eligible for an intervention-specific population. For example, a participant randomized 1:1:1 to receive 2 available interventions vs control would serve as a control for each of the interventions regardless of the matched control assigned. The primary comparison will utilize eligible participants in the intervention-specific analysis population randomized to control, regardless of the specific intervention-specific matched control that was randomized.

The randomization strategy for up to 3 contemporaneously available interventions is shown in Figure 1. Strategies for 2 interventions and for 1 intervention are shown in Figure 2 and Figure 3, respectively.

This randomization strategy can easily be generalized beyond 3 contemporaneously available interventions and will ensure approximately equal randomization of each intervention to control, while helping to maintain blinding and minimize possible bias.

Participants randomized to rivaroxaban or control under the principles listed above will be assigned to the rivaroxaban-specific analysis population.

Figure 1: Randomization for sites where 3 interventions are being studied

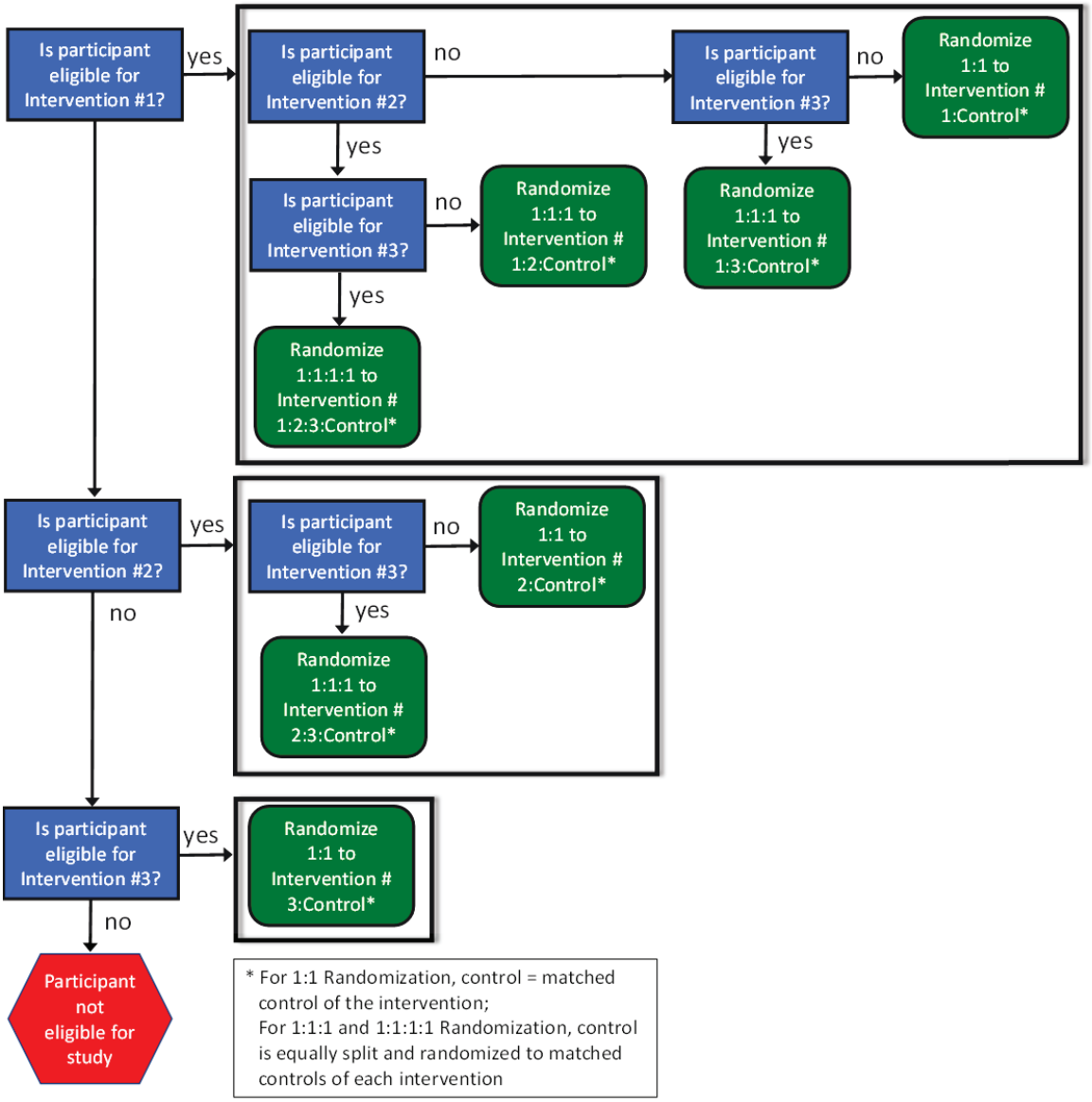


Figure 2: Randomization strategy for sites where 2 interventions are being studied

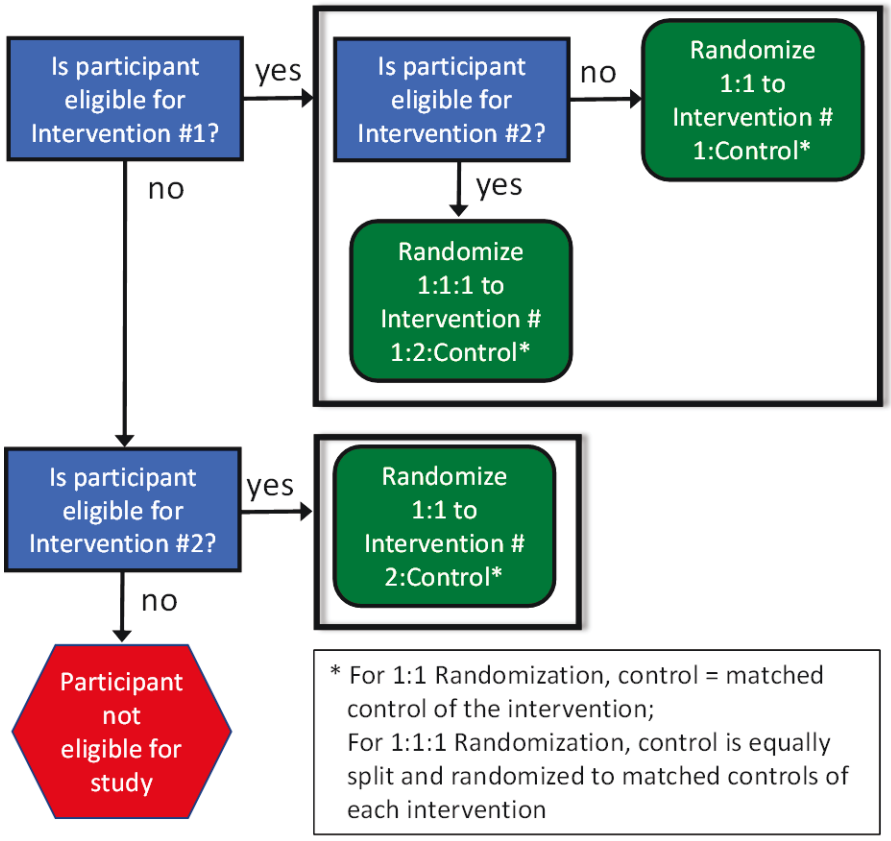
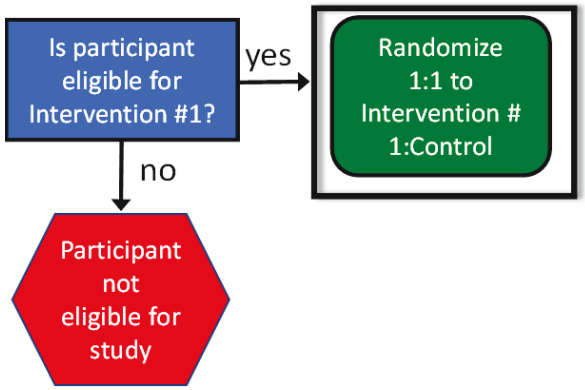


Figure 3: Randomization strategy for sites where only 1 intervention is being studied



8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

Not applicable.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 Determination of Sample Size

9.1.1 Efficacy

The total number of participants planned to be enrolled is approximately 600 (300 per group). If the true control rate for progression to moderate or severe category or greater is at least 30%, 294 participants per group will result in 80% power when the true study intervention effect is 35% as a relative decrease of rate progression, i.e., a true rivaroxaban rate of progression of 19.5% is 35% lower than that of a true placebo-control rate of progression of 30%. This sample size accounts for a drop-out rate of 10% and a 1-sided Type I error rate of 2.5%. To account for one planned interim futility analysis without adversely affecting the statistical power, the sample size was increased to 300 per group.

9.1.2 Safety

With 300 participants in the rivaroxaban intervention group, there is 80% probability to observe at least 1 SAE related to rivaroxaban when the true SAE rate is at least 0.54%.

9.2 General Conventions

Frequency (n) and percentages (%) will be used to summarize categorical variables; mean, standard deviation (SD), median, minimum, and maximum will be used to summarize continuous variables.

Decimal precision for summary statistics of continuous variables will be based on the mean value. Typically, the mean will contain 1 more decimal place than actual values but the decimal precision may vary in order to obtain an organized and understandable table or listing. The median will contain the same number of decimal places as the mean, the SD will contain 1 more decimal place than the mean, and the minimum and maximum will contain 1 less decimal place than the mean.

Unless otherwise specified, the denominators for percentages will be the number of participants in each intervention group with non-missing data for the variable of interest.

The day of receiving first dose of study intervention is defined as Study Day 1 or Day 1. All other study days will be computed relative to Day 1. For events on or after Day 1, study day for a particular event or visit will be calculated as $\text{Date}_{event} - \text{Date}_{Day\ 1} + 1$. For events before Day 1, study day for a particular event will be calculated as $\text{Date}_{event} - \text{Date}_{Day\ 1.}$ Day 0 will not be used.

9.3 Baseline definition

Unless otherwise specified, Baseline is defined as the last non-missing assessment (scheduled or unscheduled) prior to the first dose. In the case where the last non-missing assessment and the first dose coincide (i.e., assessments on Day 1), that assessment will be considered pre-intervention (Baseline).

9.4 Stratification Factor

The variable associated with the stratification factor of number of days since onset of symptoms at time of randomization [original protocol (<3 days or ≥3 days); protocol amendment 1 (<6 days or ≥6 days)] will be defined according to data from the IVRS/IWRS. If there are any participants who are identified as being miss-stratified (i.e. randomized to the incorrect strata), a sensitivity analysis of the primary analysis will be carried out using the derived stratification variable for number of days since onset of symptoms at time of randomization. As discussed in section 6 participants enrolled under the original strata will be analyzed under the derived stratification variable for number of days since onset of symptoms at time of randomization (<6 days or ≥6 days).

9.5 Handling of Missing Data

Missing and partial dates of prior and concomitant medications and adverse events will be imputed to determine the relationship between the start date of the event and the first dose date of study drug. The imputation rules provided in Appendices 2 and 3.

Statistical methods to address missing data for efficacy endpoints are provided in Section 11.

9.6 Pooling Strategy for Study Sites

Randomization will be stratified by site. Generally, all sites will be pooled by intervention for analysis purposes. Summaries by site will be included for relevant endpoints. Details are provided in the relevant sections.

9.7 Visit Windows/Unscheduled Visits

Visit windowing in general will not be applied. Unscheduled visits will not be included in by-visit summaries or analysis, but may contribute to the Baseline value and worst post-baseline assessments. In the case of a retest (same visit number assigned), the latest available test result as provided in the data transfer for that visit/time point will be used for by-visit summaries.

10 STATISTICAL ANALYSIS METHODS

10.1 Subject Disposition

All participants who provide informed consent will be accounted for in this study.

The number of participants screened, number of screening failures, and the number of participants randomized will be summarized for all screened participants per site and overall.

The following disposition and withdrawals (including reasons for intervention and study discontinuation as provided on the eCRF) will be summarized by intervention group:

- The number of participants who are randomized
  - The number of participants who are randomized and not treated
  - The number of participants who are randomized and treated
- The number of participants who completed the intervention period
- The number of participants who discontinued study intervention
- The number of participants who completed the study
- The number of participants who discontinued the study

In addition, number and percentage of participants in each analysis population, reason(s) for exclusion from each analysis population and critical and major protocol deviations will be summarized and listed for the randomized analysis population.

10.2 Demographics and Baseline Characteristics

Demographic data and other baseline characteristics will be summarized using descriptive statistics only, for the ITT, and Safety population. The denominators for percentages will be the number of participants in each intervention group with non-missing data available for the variable of interest.

Explicitly the following characteristics will be summarized:

- Age (years)
- Age groups (<65 years, ≥65 years; and 18 to <35 years, 35 to <50 years, 50 to <65 years, 65 to <75 years, ≥75 years)
- Sex (Male, female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Mixed Race, Other, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI groups (<35 kg/m^2, ≥35 kg/m^2)

  BMI (kg/m^2) will be calculated using the following formula:

$$BMI = \frac{weight\ (kg)}{height\ (m) \times height\ (m)}$$

- Presence of comorbidities factors at randomization
  - Age (<65 years, ≥65 years)
  - Presence of chronic pulmonary disease, COPD, pulmonary hypertension (Yes, No)
  - Diabetes mellitus (type 1 or type 2) requiring medication or insulin (Yes, No)
  - Hypertension, requiring at least 1 oral medication for intervention (Yes, No)
  - Immunocompromised status due to disease (Yes, No)
  - Immunocompromised status due to medication (Yes, No)
  - Chronic disease associated with high risk for severe COVID-19 (Yes, No)
  - BMI groups (<35 kg/m^2, ≥35 kg/m^2)
- Number of days since onset of symptoms at time of randomization [continuous and categorical: original protocol (<3 days or ≥3 days); protocol amendment 1 (<6 days or ≥6 days); and across both protocol versions (<6 days or ≥6 days)]
- Number of days since onset of symptoms at time of Day 1 [continuous and categorical: (<6 days or ≥6 days), where this is calculated as date of Day 1 – date of onset of symptoms + 1.
- SARS-CoV-2 diagnostic test at Day 1 (Positive, Negative)
- Gates MRI and WHO clinical assessment status at Day 1 (applicable categories)
- Oxygen saturation at Day 1
- COVID-19 signs and symptoms, participants with at least 2 symptoms, 3 symptoms, 4 symptoms, etc. at Day 1. Categories will not be mutually exclusive (i.e., patients having at least 3 symptoms will also be summarized in the at least 2 symptoms category).
- COVID-19 signs and symptoms at Day 1: each symptom (Yes, No)
- Alcohol and non-medical illicit drugs use in the last month (Yes, No)

10.3 Treatment Compliance and Exposure

Treatment compliance and exposure will be summarized for the Safety population.

Treatment compliance information for study drug will be collected through counts of remaining tablets in the bottle at the EOT or discontinuation of study drug. Compliance is computed as the number expected to be taken at time of EOT or discontinuation of study drug minus number remained +1 (as there is an extra tablet in a bottle) relative to the number expected to be taken will be summarized. The frequency and percentage of participants in each of the following categories will be presented: <50%, ≥50% and <75%, ≥75% and <100%, and >100% by study intervention group.

Any days that participants administered a dose of study drug will be tabulated for number of days exposure to study drug. Number of days exposure will be summarized as both continuous and categorical variables by study intervention group. For categorical presentation, the frequency and percentage of participants in each of the following categories will be presented: ≤7 days, 8 to ≤14 days, 15 to ≤24 days.

11 EFFICACY PARAMETERS

The primary efficacy endpoint is the proportion of participants who progress to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) at any day through Day 28.

Secondary efficacy endpoints include:

- Time to disease resolution, defined as symptoms resolution only (new onset COVID-19 symptoms resolved, and pre-existing symptoms returned to baseline) through Day 28
- Time to disease resolution, defined as 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
- Proportion of participants who progress to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) at Days 8, 14, and 21
- Proportion of participants who achieve disease resolution, defined as symptoms resolution only, at Days 8, 14, 21 and 28
- Proportion of participants who achieve disease resolution, defined as both viral clearance and symptoms clearance, at Days 8, 14, 21 and 28
- Gates MRI scale score at Days 8, 14, 21, and 28
- WHO ordinal scale score at Days 8, 14, 21, and 28
- Incidence of hospitalization through Days 8, 14, 21, and 28
- Number of days of hospitalization through Days 8, 14, 21, and 28

Exploratory endpoints include:

- Quantity (and change from baseline) of SARS-CoV-2 virus at Days 8, 14, 21 and 28
- Phylogenetic relationships of SARS-CoV-2 viruses sequenced from positive nasal swab samples

11.1 Primary Analysis

11.1.1 Estimand

The treatment policy estimand with respect to the primary efficacy objective is defined by the following:

Population: Participants in the ITT population.

Patient-level outcome: Binary outcome of progression to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) at any day through Day 28.

Intercurrent events: The following intercurrent events to be taken into account:

1. If a death occurs on or prior to Day 28, the participant will be considered as having progression to moderate or severe category (Gates MRI ordinal scale ≥3) through Day 28.

2. If hospitalization occurs on or prior to Day 28, the participant will be considered as having progression to moderate or severe category (Gates MRI ordinal scale ≥3) through Day 28.

3. If a participant is lost to follow-up on or prior to Day 28, the last observed Gates MRI ordinal scale status evaluation will be carried forward onward to Day 28.

4. If a participant discontinues the study prior to initiation of IP dosing on Day 1 (for any reason: lost to follow-up, progression to moderate or severe COVID-19, withdrawal of consent) and no Gates MRI ordinal scale assessment is available, the participant will be considered as having progression to moderate or severe category (Gates MRI ordinal scale ≥3) through Day 28.

Participants who discontinue study intervention will be followed at least until end of study, Day 35.

Population-level summary measure: Proportion of participants who progress to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) at any day through Day 28.

The primary efficacy analysis will be conducted in the ITT population. Participants randomized to rivaroxaban will be compared to participants randomized to placebo. For the primary efficacy analysis, the following primary hypothesis will be tested: Prophylactic treatment with rivaroxaban will reduce progression to moderate or severe disease category or greater (Gates MRI ordinal scale ≥3) relative to placebo in high risk participants with mild COVID-19.

The proportion of participants who have progression of COVID-19 at any time up to and including Day 28 and the corresponding 2-sided 95% CI, computed using the Mid-p method, will be summarized for the study intervention and control. The absolute difference in the risk of progression of COVID-19 and the corresponding 2-sided 95% CI will be assessed using the

stratified Miettinen and Nurminen method [Miettinen, 1985] with the Cochran-Mantel-Haenszel (CMH) weights [Lu, 2008], stratified by number of days since onset of symptoms at time of randomization (<6 days or ≥6 days). The point estimates and variance estimated for each stratum j using the Miettinen and Nurminen method are defined as

$$\hat{d}_j = \hat{p}_{1j} - \hat{p}_{2j}$$

where $\hat{p}_{1j}$ and $\hat{p}_{2j}$ are the proportions of participants in rivaroxaban and placebo group who had progression of COVID-19 through Day 28, respectively, and

$$\widetilde{Var}_j(\delta) = \left(\frac{n_j}{n_j - 1}\right)\left(\frac{\tilde{p}_{1j}(\delta)\left(1 - \tilde{p}_{1j}(\delta)\right)}{n_{1j}} + \frac{\tilde{p}_{2j}(\delta)\left(1 - \tilde{p}_{2j}(\delta)\right)}{n_{2j}}\right)$$

where $n_j = n_{1j} + n_{2j}$, and $\tilde{p}_{1j}(\delta)$ and $\tilde{p}_{2j}(\delta)$ are the maximum likelihood estimates of rivaroxaban and placebo proportions under the restriction that the risk difference is δ. For the hypothesis specified, $\delta = 0$. The maximum likelihood estimates of p_{1j} and p_{2j}, subject to the constraint that the risk difference is δ, are computed as

$$\tilde{p}_{1j}(\delta) = 2u\ \cos(w) - b/3a \quad \text{and} \quad \tilde{p}_{2j}(\delta) = \tilde{p}_{1j}(\delta) + \delta$$

where

$$w = (\pi + \cos^{-1}(v/u^3))/3$$
$$u = sign(v)\sqrt{b^2/(3a)^2 - c/3a}$$
$$v = b^3/(3a)^3 - bc/6a^2 + d/2a$$
$$a = 1 + \theta$$
$$b = -(1 + \theta + \hat{p}_{1j} + \theta\hat{p}_{2j} + \delta(\theta + 2))$$
$$c = \delta^2 + \delta\left(2\hat{p}_{1j} + \theta + 1\right) + \hat{p}_{1j} + \theta\hat{p}_{2j}$$
$$d = -\hat{p}_{1j}\delta(1 + \delta)$$
$$\theta = n_{2j}/n_{1j}$$

The CMH weights will be used to combine the point estimates and variance estimates that are calculated within each stratum using the Miettinen and Nurminen method.

$$\hat{d} = \sum_j w_j\, \hat{d}_j$$

$$\widetilde{Var}(\delta) = \sum_j w_j^2\, \widetilde{Var}_j(\delta)$$

where CMH weights, w_j, are defined as

$$w_j = W_j / \sum_k W_k$$

where

$$W_j = \left(\frac{1}{n_{1j}} + \frac{1}{n_{2j}}\right)^{-1}$$

A score-based test statistic for the null hypothesis is that the risk difference equals δ can be expressed as

$$Z(\delta) = (\hat{d} - \delta) / \sqrt{\widetilde{Var}(\delta)}$$

The 95% confidence interval for the risk difference consists of all values of δ for which the score test statistic $Z(\hat{\delta}_L) = z_{1-\alpha/2}$ and $Z(\hat{\delta}_U) = -z_{1-\alpha/2}$, where $z_{1-\alpha/2}$ is the $(1 - \alpha/2)$ percentile of the standard normal distribution, and $\hat{\delta}_L$denotes the lower limit and $\hat{\delta}_U$ denotes the upper limit.

For participants who are lost to follow-up prior to Day 28, the last disease status evaluation will be used as last observation carried forward to Day 28 to address the missing visit data in the primary analysis.

11.1.2 Sensitivity Analyses

To assess the robustness of the primary results, analyses will be repeated for the primary analysis using the mITT and PP populations.

Sensitivity analysis will be performed according to their derived actual strata instead of the randomized strata.

In case any participants use any prohibited concomitant use of medication prior to treatment discontinuation and day 28, they will be flagged as significant protocol deviations and excluded from the per-protocol efficacy analyses.

11.1.3 Subgroup Analysis

In order to assess the consistency of treatment benefit with respect to the primary efficacy endpoint, forest plots and summary tables will be provided for the following subgroups:

- Race (White, Black, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Sex (Male, Female)
- Number of days since onset of symptoms at time of randomization (<6 days or ≥6 days)

- Comorbidities and risks consist of the following:
  - Age (<65 years, ≥65 years)
  - Presence of chronic pulmonary disease, COPD, pulmonary hypertension (Yes, No)
  - Diabetes mellitus (type 1 or type 2) requiring medication or insulin (Yes, No)
  - Hypertension, requiring at least 1 oral medication for intervention (Yes, No)
  - Immunocompromised status due to disease or medication (Yes, No)
  - Chronic disease associated with high risk for severe COVID-19 (Yes, No)
  - BMI groups (<35 kg/m^2, ≥35 kg/m^2)

11.2 Secondary Analysis

Secondary analyses will be conducted in the ITT population. Sensitivity analyses of secondary analyses will be performed using the mITT and PP populations, to assess the robustness of the secondary results.

11.2.1 Estimand

The treatment policy estimand with respect to the secondary efficacy objective is defined for the key secondary endpoints by the following:

Population: Participants in the ITT population.

Patient-level outcome: Time to disease resolution through day 28.

Intercurrent events: The following intercurrent events to be taken into account:

1. If a death occurs prior to Day 28, the participant will be considered as not having disease resolution through Day 28 (i.e., censored at Day 28).
2. If a participant is lost to follow-up prior to Day 28, the participant will be considered as not having disease resolution and will be censored at the time of lost to follow-up.
3. If a participant discontinues the study [for any reason: lost to follow-up, progression to moderate or severe COVID-19 (or worse), withdrawal of consent] prior to initiation of IP dosing on Day 1 and no symptoms resolution assessment is available, the participant will be considered as not having disease resolution and will be censored on Day 1.

Participants who discontinue study intervention will be followed at least until end of study, Day 35.

Population-level summary measure: Median time to disease resolution.

11.2.2 Disease Resolution

11.2.2.1 Time to Disease Resolution (Symptoms Resolution)

Disease resolution is defined as symptoms resolution (new onset coronavirus disease 2019 (COVID-19) symptoms resolved, and pre-existing symptoms returned to baseline) through Day 28. For the time to disease resolution analysis, the following hypothesis will be tested: prophylactic treatment with rivaroxaban will increase the rate of time to disease resolution relative to placebo in high risk participants with mild COVID-19.

Time to disease resolution is defined as the time from first dose to the date of symptoms resolution (as determined by the investigator: has the participant's COVID-19 signs and/or symptoms resolved or returned to baseline). The following rules (Table 3) will be used to define time to disease resolution:

Table 3: Censoring rules for time to disease resolution.

Situation	Outcome	Date of event/censoring
Death for any reason	Censored	Day 28
Discontinued prior to Day 28 without disease resolution	Censored	Date of last disease resolution assessment
No disease resolution through Day 28	Censored	Day 28
Randomized, treated but no post-baseline assessments available	Censored	Day 1
Disease resolution through Day 28	Event	Initial date of last sequence of consecutive disease resolution.
Discontinued prior to Day 28 with disease resolution at last assessment	Event	Initial date of last sequence of consecutive disease resolution.
Randomized, not treated	Censored	Date of randomization

*sequence = a series of one or more disease resolutions with no progression.

Example scenarios are included in Table 4 for reference.

Table 4: Example scenarios for time to time to disease resolution.

Time point	Day 1	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14	Day 18	Day 21	Day 24	Day 28	Endpoint
Participant 1	N	N	N	N	N	N	N	N	N	N	N	No DR, censored at Day 28
Participant 2	N	Y	N	N	N	N	Died					No DR, censored at Day 28
Participant 3	N	Y	Y	N	N	N	Disc.					No DR, censored at Day 12
Participant 4	N	Y	N	N	N	Y	Y	Y	Y	Y	N	DR at Day 12*
Participant 5	N	Y	Y	N	N	Y	Y	Y	Disc.			DR at Day 12
Participant 6	N	N	Y	Y	N	N	Y	Y	Y	Y	Y	DR at Day 14
Participant 7	N	N	N	N	N	N	N	N	N	N	Y	DR at Day 28
Participant 8	N	N	N	N	N	Y	Y	Y	Y	N	N	No DR, censored at Day 28**
Participant 9	N	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	DR at Day 4
Participant 10	N	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	No DR, censored at Day 1
Participant 11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	DR at Day 1
Participant 12	N	Y	N	N	N	Y	Y	N	Disc.			No DR, censored at Day 18

* Due to consecutive days with disease resolution and followed by a day with no disease resolution as the last assessment.
**Due to consecutive days with no disease resolution occur after days with disease resolution.
DR = disease resolution. N=no; Y=yes. NA=Not available.

For time to disease resolution, a stratified 1-sided log-rank test, stratified by number of days since onset of symptoms at time of randomization (<6 days or ≥6 days), will be used to compare between the study intervention and control. The Kaplan-Meier method will be used to obtain the estimates of medians with the associated 2-sided 95% CIs of time to disease resolution,

computed using Brookmeyer and Crowley method. A stratified Cox proportional hazards model, stratified by number of days since onset of symptoms at time of randomization (<6 days or ≥6 days) will be used to estimate the hazard ratio and the corresponding 2-sided 95% CI associated with the rate of disease resolution for the study intervention relative to control.

Due to anticipated heterogeneity in the rate of disease resolution, pre-specified baseline variables, including age and BMI will be included in the model to increase precision. Including time-dependent variables, i.e., log(time)-by-variables interactions, to the model to fit a stratified Cox non-proportional hazards model to assess the proportional hazards assumption. If the coefficients for the time-dependent variables are not statistically different from zero based on a chi-square test with 1 degree of freedom would suggest that proportional hazards assumption is adequate for all variables included in the model.

11.2.2.2 Time to Disease Resolution (Symptoms Resolution and Viral Clearance)

Time to disease resolution that is defined as 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 will be analyzed as similarly to that described for time to disease resolution that is defined as symptoms resolution. Participants who have completed Day 21 visit but not Day 35 visit and did not have two consecutive negative tests at the time of study stop will be censored at the time of their last visit.

11.2.2.3 Subgroup Analysis

Analysis of key secondary endpoints will be repeated for the subgroups as specified in Section 11.1.3. Forest plots will be provided.

11.2.3 Proportion of Participants with Disease Resolution

The proportions of participants who achieve disease resolution defined as symptom resolution at Days 8, 14, 21, and 28 will be summarized for the study intervention and control. The 2-sided 95% CI for the proportion will be computed using the Mid-p method. The absolute difference in the proportion and the corresponding 2-sided 95% CI of participants achieving disease resolution defined as symptom resolution at any time up to and including Days 8, 14, 21, and 28 between the study intervention and control will be assessed using the stratified Miettinen and Nurminen method, stratified by number of days of symptoms at time of randomization (<6 days or ≥6 days).

In addition, the proportions of participants who achieve disease resolution defined as symptom resolution and viral clearance (2 consecutive negative diagnostic tests) at any time up to and including Days 8, 14, 21, and 28 will be summarized and analyzed as similar to that described for the proportions of participants who achieve disease resolution defined as symptom resolution only.

11.2.4 Disease Progression of COVID-19

The proportion of participants who progress to moderate or severe disease category or higher (Gates MRI ordinal scale ≥3) at any time up to and including Days 8, 12, and 21 will be summarized and analyzed for the study intervention and control as similar to that described for proportion of participants who progress to moderate or severe disease category or higher through Day 28.

11.2.5 Gates MRI Scale Scores

Table 5: Gates MRI Ordinal Scale Clinical Endpoint Definitions

Scale	Category	Endpoint definition
1	Asymptomatic/symptoms similar to pre-COVID-19 status	• No symptoms and signs AND • No limitation of daily activities
2	Mild	• Symptomatic AND • No shortness of breath AND • No hypoxemia (O_2 saturation ≥94% in ambient air)
3	Moderate or severe	• Symptomatic AND • Shortness of breath* OR tachypnea (respiratory rate ≥20 min)* OR hypoxemia (<94% in ambient air)*
4	Critically ill	• Symptomatic AND • Receiving high flow oxygen OR non-invasive mechanical ventilation
5	Critically ill with invasive mechanical ventilation or extra pulmonary complication	• Symptomatic AND • Receiving invasive mechanical ventilation OR Life threatening or debilitating extra pulmonary complications
6	Critically ill with Extra-Corporeal Membrane Oxygenation (ECMO)	• Symptomatic AND • Receiving ECMO
7	Death	• Death

*For known COPD participants, moderate or severe category requires worsening of shortness of breath or medical or oxygen saturation from pre-COVID-19 status.

The distributions of the Gates MRI ordinal scale scores (defined as in Table 5) will be summarized by day and treatment group. Stacked bar plots presenting the proportion of participants in each category of Gates MRI ordinal scale at Days 8, 14, 21, and 28 for each treatment group will be provided.

11.2.6 WHO Ordinal Scale Scores

Table 6: WHO Ordinal Scale for Assessment of Clinical Status of COVID-19 Patients

Participant Status	Descriptor	Scale
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5

Hospitalized severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO2/FiO2 ≥150 or SpO2/FiO2 ≥200	7
	Mechanical ventilation pO2/FiO2 <150 (SpO2/FiO2 <200) or vasopressors	8
	Mechanical ventilation pO2/FiO2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO clinical progression scale; WHO Working group [WHO(c), 2020]
ECMO=extracorporeal membrane oxygenation; FiO2=fraction of inspired oxygen;
NIV=non-invasive ventilation; pO2=partial pressure of oxygen; RNA = ribonucleic acid; SpO2=oxygen saturation.
*If hospitalized for isolation only, record status as for ambulatory patient.

WHO ordinal scale scores (as defined in Table 6) will be summarized and analyzed for overall burden of disease and disease severity as similar to that described for Gates MRI scale scores. For the purposes of evaluating the disease severity using the proportional odds model, the log-odds of the cumulative probability of the WHO ordinal scale score ≤3 is modeled.

11.2.7 Incidence of Hospitalization

The proportion of hospitalized participants at any time up to and including Days 8, 14, 21, and 28 will be summarized for the study intervention and control with the corresponding 2-sided 95% CIs computed using the Mid-p method. The risk ratios and the corresponding 2-sided score 95% CIs associated with the incidence of hospitalization for the study intervention relative to control at any time up to and including Days 8, 14, 21, and 28 will be assessed using the stratified CMH method, stratified by number of days of symptoms at time of randomization (<6 days or ≥6 days).

11.2.8 Number of Days of Hospitalization

Number of days of hospitalization will be summarized using descriptive statistics by treatment group and number of days of symptoms at time of randomization (<6 days or ≥6 days).

11.3 Exploratory Analysis

11.3.1 SARS-CoV-2 Diagnostic Test

Proportion of participants having negative or positive SAR-CoV-2 diagnostic test will be summarized by treatment group and days since onset of symptoms at time of randomization (<6 days or ≥6 days) at Days 1, 4, 8, 14, 21, and 28. For computing percentages, the denominator will be the number of participants with a test outcome available or indicated as not done in CRF for a specific group and visit.

11.3.2 Cycle Threshold Value of SARS CoV-2 Test.

Cycle threshold value (Ct) is the number of cycles in an RT-PCR assay needed to amplify viral RNA to reach detectable level. Low Ct value represents the number of cycles in an RT-PCR assay needed to amplify viral RNA to reach a detectable level; with lower Ct values reflective of

higher viral levels. Ct will be summarized using descriptive statistics by treatment group and number of days since onset of symptoms at time of randomization (<6 days or ≥6 days) at Days 1, 4, 8, 14, 21, and 28.

Viral sequencing may be used to assess the phylogenetic relationships between SARS-CoV-2 viruses obtained from positive nasal swab samples. Phylogenetic trees will be generated to determine whether participants were part of a transmission cluster. The aforementioned analyses may be performed upon availability of SARS CoV-2 viral load data.

11.4 Independent Data Monitoring Committee

The purpose of the IDMC is to monitor the study for safety and efficacy. The IDMC may request additional information, or a pause in recruitment and dosing, while safety data are being evaluated.

The IDMC will operate according to a charter and the structure, participants, meeting information and other details will be provided in the charter. The charter will be available prior to study start.

The IDMC will meet monthly or ad hoc, if necessary, to review safety data, and may request additional information, or a pause, while safety data are being evaluated. All procedures associated with this review will be documented.

The IDMC will review the pausing guidelines that are put in place to address medical events necessitating a pause in enrollment and in participant dosing, and trigger IDMC reviews. Therefore, these guidelines are in effect during the active enrollment and dosing period. Any of the below conditions, if identified either by the study staff, investigator, the Sponsor or the IDMC, will trigger a pause of the enrollment and pause of administration of study intervention until the IDMC has reviewed the safety data and made a recommendation on how to proceed:

1. One report of anaphylaxis with or without bronchospasm within 4 hours of taking study intervention indicative of an immediate hypersensitivity reaction to the study intervention.
2. One report of major bleeding judged as related to study intervention by the investigator.

This sponsor will set up a proper firewall to ensure that those blinded are insulated from knowledge of unblinded interim results. Participants and study staff evaluating them will not be aware of the assigned treatment groups. The laboratories performing the SARS-CoV-2 diagnostic testing will be blinded. Sponsor will be blinded throughout the study conduct.

11.5 Group Sequential Design

11.5.1 Interim Analyses

An interim analysis will only include participants who have been lost to follow-up or who have completed 28 days of follow-up at the time of the data cut. A 2-stage group sequential design

will be used to assess futility at the interim analysis using a Hwang-Shih-DeCani beta spending function at 33% of the information. If the trial does not cross the pre-specified boundaries to declare futility at the interim analysis, a final efficacy and safety analysis will occur after all participants complete the study Day 35 of follow-up. The predefined gamma parameter used will be -4 for futility, which is similar to the boundaries from the O'Brien-Fleming method (O'Brien, 1979). The lower bound for futility will be binding.

Table 7 displays the Hwang-Shih-DeCani boundary information for the group sequential design with an interim analysis for futility after approximately 200 participants complete Day 28 and a final analysis for efficacy and safety after 600 participants completed Day 35. The actual boundaries used will be based on the Hwang-Shih-DeCani spending functions that reflect the actual number of participants (i.e., the actual proportion of the information) included at the time of the interim analysis.

Table 7: Example of Alpha and Binding Beta Boundaries

Boundary Information (p-Value Scale) [EAST 6 (Version 6.5)] Binding Beta Boundary				
Stage	**Information Level**		**Boundary p-values**	
	Proportion	**Number of Participants**	**Alpha**	**Binding Beta**
Interim 1	0.3333	200	NA	0.7550
Final	1.0000	600	0.0250	0.0250

If the test statistic of the interim analysis for the primary endpoint crosses the pre-specified binding futility boundary to declare futility, the study will stop enrollment, but will continue following those enrolled participants until study completion. The study will not be evaluated for efficacy at the interim analysis.

11.5.1.1 Stopping Probabilities Under Various Hypothetical References

The study design allows early stopping for futility probabilities under various hypothetical "harm" or "equal" scenarios; examples are included below using EAST 6 (Version 6.5) (number of simulations=10,000, seed=6547):

- "harm" scenario 1: If the true rivaroxaban rate of progression is 35% and the true control rate is 30%, the probability of stopping early for futility is 50.2% at the interim analysis.
- "harm" scenario 2: If the true rivaroxaban rate of progression is 19.5% and the true control rate is 15%, the probability of stopping early for futility is 51.6% at the interim analysis.
- "equal" scenario 1: If the true rivaroxaban rate of progression is 30% and the true control rate is 30%, the probability of stopping early for futility is 25.5% at the interim analysis.
- "equal" scenario 2: If the true rivaroxaban rate of progression is 15% and the true control rate is 15%, the probability of stopping early for futility is 23.0% at the interim analysis.

12 SAFETY AND TOLERABILITY

Safety analyses will be conducted in the safety population. Safety outcomes will include:

- Grade 3 AEs
- Grade 4 AEs
- AEs resulting in study intervention discontinuation
- SAEs
- AESIs (including major bleeding and severe hypersensitivity to rivaroxaban)

12.1 Adverse Events

AEs will be coded using MedDRA version 22.1 or higher. AE severity will be graded as Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Potentially Life-threatening), or Grade 5 (Death) as referencing to the specific toxicity grading by Division of Acquired Immunodeficiency Syndrome (DAIDS) AE Grading Table [DAIDS 2017].

AEs starting on or after first day of study intervention will be considered as treatment-emergent. Only AEs within the reporting window will be included within the relevant category in summary tables. All AEs will be listed, regardless of if it was reported within the applicable reporting window.

An AE overview table containing the frequency and percent of participants in each of the following categories (summarized by intervention group) and also the 95% CI (calculated for a single proportion using the Mid-p method):

- Any AE
- Related AEs
- Grade 3 AEs
- Grade 4 AEs
- AEs resulting in study intervention discontinuation
- SAEs
- AEs with outcome of death
- AESIs (including major bleeding and severe hypersensitivity to rivaroxaban)

Additionally, the following will be summarized by SOC and PT for each intervention group:

- Incidence of AEs
- Incidence of related AEs

- Incidence of Grade 3 AEs
- Incidence of Grade 4 AEs
- Incidence of AEs resulting in study intervention discontinuation
- Incidence of SAEs
- Incidence of AEs with outcome of death
- Incidence of AESIs

Summaries of SOC and PT will be sorted alphabetically by SOC and by decreasing frequency of PT in the intervention group. If a participant has more than 1 AE at a given level (e.g., SOC and PT), the participant will only be counted once within that level.

Missing severities and relationship will not be regarded as 'worst case'.

Incidences of Grade 3 AEs, Grade 4 AEs, and AEs resulting in study intervention discontinuation will be summarized by subgroups.

- Race (white, black, other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Sex (male, female)
- Number of days since onset of symptoms at time of randomization (<6 days or ≥6 days)
- Presence of comorbidities/risks
    - Age (<65 years, ≥65 years)
    - Presence of chronic pulmonary disease, COPD, pulmonary hypertension (Yes, No)
    - Diabetes mellitus (type 1 or type 2) requiring medication or insulin (Yes, No)
    - Hypertension, requiring at least 1 oral medication for intervention (Yes, No)
    - Immunocompromised status due to disease or medication (Yes, No)
    - Chronic disease associated with high risk for severe COVID-19 (Yes, No)
    - BMI groups (<35 kg/m^2, ≥35 kg/m^2)

13 OTHER RELEVANT DATA ANALYSES/SUMMARIES

13.1 Medical History

Medical history will be coded using MedDRA version 22.1 or higher. Medical history will be summarized by SOC and PT by intervention group for the Safety population and listed for the randomized population. Summaries of SOC and PT will be sorted alphabetically by SOC and by descending frequency of PT in the rivaroxaban group. If a participant has more than 1 medical

history even at a given level (e.g., SOC and PT), the participant will only be counted once within that level. A listing of medical history will also be presented.

No imputation of partial or missing dates will be performed for medical history and study days will not be presented for these cases.

13.2 Prior and Concomitant Medications

Medications will be coded using the WHO Drug Global Mar2019 or later version. A prior medication is defined as a medication with a stop date before the first dose date. A concomitant medication is defined as a medication with a stop date on or after the first dose date, thus a medication that is ongoing at the time of a participant receiving study intervention is considered concomitant. Partial and missing dates for concomitant medications will be imputed using the guidance in Appendix 2. The recorded partial/missing dates will be displayed in the listings and study days will not be presented for these cases.

Medications will be summarized by ATC level 3 and preferred name by intervention group for the Safety population. Summaries of ATC levels 3 and preferred name will be sorted alphabetically by ATC level 3 and by decreasing frequency of preferred name in the rivaroxaban group. If a participant has more than 1 medication at a given level, the participant will only be counted once at that level. Separate summaries for prior and concomitant medications will be provided.

14 REFERENCES

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6. Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health US Department of Health and Human Services (DAIDS) Regulatory Support Center. 2017. Table for grading the severity of adult and pediatric adverse events. Corrected version 2.1. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

15 APPENDICES

Appendix 1 Schedule of Assessments and Procedures

Visits	Screening (≤5 days of Day 1)	Day 1	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14	Day 18	Day 21	Day 24	Day 28	Day 35
Obtain consent	X												
Demographics, past and current medical history including known pregnancy/lactation status, and medication history	X												
Lab-confirmed SARS-CoV-2 positive diagnostic testing[1]	X												
Inclusion and exclusion criteria	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[2]	X												
Study intervention dose (Day 1 Day 21) and record adherence to dosing		X	X	X	X	X	X	X	X	X			
Clinical status assessment using ordinal scales for Gates MRI and WHO		X	X	X	X	X	X	X	X	X	X	X	
COVID-19 signs and symptoms, temperature, oxygen saturation		X	X	X	X	X	X	X	X	X	X	X	
AEs assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Bleeding events and severity assessment		X	X	X	X	X	X	X	X	X	X	X	X
Self-collection of nasal or oropharynx SARS-CoV-2 sample for diagnostic testing[3]	(X)[1]	X	X		X			X		X		X	

Note that visits will preferably take place remotely.
SARS-CoV-2= Severe acute respiratory syndrome coronavirus 2
Gates MRI= Bill & Melinda Gates Medical Research Institute
WHO = World Health Organization
[1] If there is documented positive SARS-CoV-2 diagnostic testing performed with a sample collected ≤10 days prior to screening, the test does not need to be performed. If no documentation, the potential participant will be asked to collect a nasal or oropharynx swab sample to send for testing.
[2] If documentation of a previous positive SARS-CoV-2 test is not available and a test is performed at screening, randomization will occur after a positive result is obtained.
[3] Participant will be asked to collect a sample per kit instructions. Discontinue collection during hospitalization and/or per physician's discretion when two consecutive negative results are available at any time during the study.
Note that an unscheduled visit may be required. Additional collection of a nasal swab sample may be performed based on the clinical judgement of the PI.

Appendix 2 Prior and Concomitant Medications Date Imputation

Imputation Rules for Partial Dates (D=day, M=month, Y=year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start Date	D only	M and Y same as M and Y of date of treatment	Date of treatment
		M and/or Y not the same as date of treatment	First day of month
	M and D	Y same as Y of date of treatment	Date of treatment
		Y not the same as date of treatment	Jan 01 of Y
	M, D, and Y	Non-date completely missing	Day prior to date of treatment
Stop Date	D only	M and Y same as M and Y of date of discontinuation/completion of study	Date of discontinuation/ completion of study
		M and/or Y not the same as date of discontinuation/completion of study	Last day of month
	M and D	Y same as Y of date of discontinuation/completion of study	Date of discontinuation/ completion of study
		Y not the same as date of discontinuation/completion of study	Dec 31 of Y
	M, D, and Y	None – date completely missing and NOT ongoing	Date of discontinuation/ completion of study

Appendix 3 Adverse Events Dates Imputation

Date	Situation	Imputation Rule
AE Start Date	Only month and year are known and month is prior to first dose date	Use the first day of the month
	Only month and year are known and month is the same as first dose date	Use the first dose date
	Only month and year are known and month is after first dose date	Use the first day of the month
	Only year is known and year is after first dose date	Use Jan 1 of that year
AE End Date	Only month and year are known and month is prior to last dose date	Use the last day of the month
	Only month and year are known and month is the same as last dose date	Use the last dose date
	Only month and year are known and month is after last dose date	Use the first day of the month
	Only year is known and year is before last dose date	Use Dec 31 of that year
	The estimated stop date is before a complete or imputed AE start date	Use the last day of the month of the AE start date

AE = adverse event

Note: The imputation of end date must be later than start date.

Appendix 4 SAS Code

Appendix 5 Document History

DOCUMENT HISTORY	
Document	**Date**
Original SAP (Version 1.1):	14 Dec 2020
Amendment 1 (Version 1.2)	27 Jan 2021
Amendment 2 (Version 2.0)	11 Feb 2021

Changes in Version 1.2:

Following protocol Version 4, Amendment 2, the SAP was revised to match the protocol changes as follows:

- The second interim analysis is removed from the group sequential design. The first interim analysis will be used to assess futility and the final analysis will be used to assess efficacy and safety.
- The Hwang-Shih-DeCani spending function is re-computed for a group sequential design that plans for one interim analysis to assess futility and a final analysis to assess efficacy and safety.
- Re-computing the stopping probabilities under various hypothetical references based on the revised group sequential design.

Changes in Version 2.0:

The Gates MRI-COD-01-T01 was discontinued early on February 4, 2021 based on the recommendation of the IDMC after reviewing the interim data on January 28 and February 3, 2021. Changes to efficacy analyses to account for participants who discontinued study intervention due to study discontinuation.

- Define final efficacy population for final efficacy analyses
- Omit sensitivity analyses #1 through #3 for the primary endpoint
- Omit summary tables of subgroup analyses for the key secondary endpoints
- Omit sensitivity analysis of applying different censoring rule for time to event analysis of the key secondary endpoints
- Omit proportional odds model for COVID-19 clinical status measured by Gates MRI ordinal scale
- Omit MMRM analysis of Gates MRI ordinal scale

- Omit ANCOVA of overall burden of disease based on Gates MRI ordinal scale
- Omit ANCOVA of maximum post-baseline Gates MRI score
- Omit proportional odds model for COVID-19 clinical status measured by WHO ordinal scale
- Omit MMRM analysis of WHO ordinal scale
- Omit ANCOVA of overall burden of disease based on WHO ordinal scale
- Omit ANCOVA of maxium post-baseline WHO score
- Omit negative binomial model for number of days of hospitalization
- Omit linear mixed effects model for cycle threshold values of SAR CoV-2 diagnostic test