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A RANDOMIZED, DOUBLE-BLIND, SHAM CONTROLLED, STRATIFIED, PIVOTAL EFFICACY AND SAFETY STUDY OF THE EMITBIO RD-X19 TREATMENT DEVICE IN INDIVIDUALS 40 YEARS OF AGE AND OLDER WITH MILD COVID-19 IN THE AT-HOME SETTING

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STATISTICAL ANALYSIS PLAN

VERSION 2.0

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STATISTICAL ANALYSIS PLAN FOR

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Section 1. ABBREVIATIONS & DEFINITIONS

ABBREVIATIONS

ANCOVA Analysis of covariance

ATC Anatomical therapeutic chemical

BMI Body mass index

BRFS Baseline risk factor score

CI Confidence interval

CRF Case report form

DCT Decentralized clinical trial

DR-TEAE Device-related treatment-emergent adverse event

DR-TESAE Device-related treatment-emergent serious adverse event

ET Early termination

FAS Full analysis set

FDA Food and Drug Administration (USFDA)

GCP Good Clinical Practice

ICH International Council for Harmonisation

LOD Limit of detection

Ltd Limited

LLOQ Lower limit of quantification

MedDRA Medical Dictionary for Regulatory Affairs

NPANCOVA Non-parametric ANCOVA

PH Proportional hazards

PI Principal investigator

PP Per protocol

PT Preferred term

RR Respiration rate

SAE Serious adverse event

SAP Statistical Analysis Plan

SOC System organ class

SOP Standard operating procedure

SpO_2 Oxygen saturation

TEAE Treatment emergent adverse event

TESAE Treatment emergent serious adverse event

ULOQ Upper limit of quantification

Section 2. INTRODUCTION & TERMS

2.1. INTRODUCTION

This document describes the statistical analysis and reporting plan for data from *A Randomized, Double-Blind, Sham Controlled, Stratified, Pivotal Efficacy and Safety Study of the EmitBio RD-X19 Treatment Device in Individuals 40 Years of Age and Older with Mild COVID-19 in the At-Home Setting* [1].The primary goal of the study is to evaluate the safety and efficacy of the RD-X19 treatment device to provide sufficient evidence to FDA to justify the authorization and/or approval of the device for treatment of subjects with mild COVID-19, age 40 and older in the home setting.

As described in the ICH E9 guidelines [2], [3] the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the study protocol [1], and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

Details of the procedures that will be followed by Quantics when undertaking data receipt, analysis and reporting are described in Quantics SOPs [4] and [5].

Any amendments to the SAP will be made prior to database lock.

Any additional analyses not described in the final SAP or deviations from the final SAP will be documented in the clinical study report.

Quantics Consulting Limited will perform the statistical analyses and are responsible for the production and quality control of all tables, listings, and figures.

Section 3. STUDY OBJECTIVES AND DESIGN

3.1. STUDY OBJECTIVES

The primary goal of the study is to establish the efficacy and safety of the RD-X19 light dosing treatment device to treat eligible subjects who have mild COVID-19 (based on the NIH and FDA definition of mild COVID-19) with sufficient data to support a regulatory filing for authorization and approval by FDA. Specifically:

- Safety objective:
  - To assess device-related Serious Adverse Events (SAEs) and Treatment Emergent Adverse Events (TEAEs), including local site reactions.
- Effectiveness objectives:
  - To assess the reduction in time to sustained resolution of COVID-19 signs and symptoms (without subsequent symptom recurrence or disease progression until the end of the study) with the RD-X19 device compared with a sham device.
  - To assess the reduction in time to the first of two consecutive negative SARS-CoV-2 antigen tests (without subsequent virological rebound during the subjects' remaining time on study) when using the RD-X19 device compared with a sham device.

3.2. STUDY DESIGN

This is a randomized, double blind, sham controlled study of the EmitBio RD-X19 light dosing treatment device. 326 subjects will be randomized at a 1:1 ratio into RD-X19 treatment and sham device treatment groups.

Subjects will be aged 40-years-old or over on the date of enrollment, have a positive COVID-19 test with time since symptom onset of 72 hours or less, and meet the NIH and FDA definition of mild COVID-19. For randomization, subjects will be stratified by age (categories 40-49 years and ≥50 years) and baseline disease severity score[1] (< 1.25, ≥ 1.25).

Subjects will be treated for 7 days and followed up for a further 7 days after the end of treatment (i.e., subjects will spend 14 days on the study in total).

3.3. DETERMINATION OF SAMPLE SIZE

The sample size was based on the primary end point of time to sustained symptom resolution. In the EB-P20-01 trial, for subjects aged 40-years-old or over with mild disease (based on the NIH and FDA definition of mild COVID-19), the hazard ratio for this endpoint in

[1] The COVID-19 Composite Severity Score at baseline is defined as the sum of the eight individual COVID-19 symptom severity scores divided by eight.

the full analysis set (FAS) was 0.62. Assuming an overall (one-sided) type 1 error of 0.025, a total of 228 events for the primary endpoint gives 95% power for a hazard ratio of 0.62 and also gives 90% power for a hazard ratio of 0.65, as well as 80% power for a hazard ratio of 0.69.

A total of 326 subjects will be initially randomized 1:1 (to RD-X19 and Sham) which will result in approximately 228 events assuming that 90% of RD-X19 subjects and 50% of Sham subjects will have the event.

A blinded sample size review will be carried out by an independent statistician based on the first 164 randomized subjects, with the objective of seeing whether the sample size needs to be increased. See Section 8.1 for details.

3.4. STUDY VISITS

Baseline visit: Subjects will be screened, enrolled and randomized at the baseline visit on study day 1. Objective clinical assessments (vital signs, a complete physical exam, oropharyngeal exams) will be made by study staff.

Daily days 1 to 7: Study subjects will self-administer treatment twice daily, 5 minutes per treatment for 7 consecutive days. They will also self-assess for nine pre-specified COVID-19 sign and symptoms, perform a SARS-CoV-2 rapid antigen test and measure oxygen saturation twice a day, recorded using an e-diary. TEAEs will be ascertained (both solicited and unsolicited) by study staff during clinical site visits. While not specifically queried by the IQVIA decentralized clinical team members during a tele-visit, study subjects may report a treatment-emergent adverse event (TEAE) during the televisit or by contacting the clinical site at any time. DCT staff will make personal contact with study participants (via tele-visit) twice a day on each of these first seven days in order to ensure compliance with the treatment, SARS-CoV-2 rapid antigen testing, COVID-19 symptom severity scoring and measurement of oral temperature and oxygen saturation (SpO_2). Subjects will return to the clinical site on study day 5(+/-1), or for early termination, for assessment by study staff and principal investigator (PI) or an appropriately credentialed delegated sub-investigator.

Daily days 7 to 14: No treatment but e-diary entries continue. Study staff will make personal contact with study participants, as required, to ensure all study procedures are completed. Study subjects will return to the clinical site on study days 8(+/-1) and 14(+/-2), or for early termination, for assessment by study staff and PI or an appropriately credentialed delegated sub-investigator. There must be a minimum of 48 hours between Day 5 and Day 8 clinic visits.

Section 4. STUDY ENDPOINTS

4.1. PRIMARY ENDPOINT

The primary endpoint is the time to sustained resolution of COVID-19 signs and symptoms without subsequent symptom recurrence or disease progression (until the end of the study), measured in hours from time of randomization.

The first step in derivation of the primary endpoint is via the twice-daily assessments where the subject records signs and symptoms in the e-diary. Each of the eight symptoms (cough, sore throat, nasal congestion, headache, chills and/or sweats, myalgia, fatigue, and nausea (with or without vomiting) are classified as one of:

None (Grade 0)	Symptom not present
Mild (Grade 1)	No influence on daily activities
Moderate (Grade2)	Noticeable influence on daily activities
Severe (Grade 3)	Daily activities not possible

The single sign incorporated in the first step in derivation of the primary endpoint (see below) is whether or not oral temperature is greater than or equal to 100.5°F.

Note: Inclusion criterion 3 for the study requires that subjects have at least two moderate or greater for the eight symptoms, or one moderate or greater for these symptoms and fever (temperature ≥ 100.5°F).

In addition, oral temperature and oxygen saturation ($Sp0_2$) are self-measured twice daily by subjects and recorded in the e-diary. Each is measured three times (over 10 minutes); the analysis quantity will be the mean of these repeated measures. If fewer than three repeated measures are taken on a given occasion, the analysis quantity continues to be their mean. Respiration rate (RR) is measured on clinic visit days.

Note: For the first assessment, information to make the below classifications is collected twice, once as part of the baseline visit and once self-reported in the subject's e-diary. When classifying subjects for this timepoint, use the information collected as part of the baseline visit (CRFs: 'Covid-19 testing and symptoms' and 'Vital signs')

Based on this, each timepoint/assessment can then be classified in the following manner:

i. **Success (S)** corresponds to resolution i.e. if all of the eight symptoms are graded with a severity score of 0 (absent) or 1 (mild), and the subject's oral temperature < 100.5°F.
ii. **Failure (F_n)** corresponds to n ≥1 of the nine signs and symptoms not meeting the condition described in (i) above.

iii. **Disease progression (D)** corresponds to the subject having respiration rate (RR) ≥ 20/min and SpO_2 < 96%. Both measures are based on the average of three replicate assessments over a 10-minute period. Additionally, disease progression will be classified as having occurred if pulmonary imaging demonstrates COVID-19 pneumonia based on an attended medical visit recorded on a medically-attended visit CRF or an AE/SAE report.

iv. **Missing (M)** corresponds to the subject not recording all sign and symptom entries in their e-diary at this timepoint.

Note: At baseline a subject would be "F_n" with n ≥ 2, unless a subject did not satisfy inclusion criterion #3.

For subjects with sign/symptom data missing at a particular timepoint, data handling rules are as follows.

(1) Subjects who do not input data for any signs or symptoms at a particular assessment will be assigned code “M” (missing) at that assessment, as described above.
(2) Subjects who input data for some but not all signs and symptoms at a particular assessment will be handled as follows:
    a. If *any* of the signs and symptoms for which data was provided *do not* meet the resolution condition described in (i) above, then the subject will be assigned code F_n (failure to achieve symptom resolution for "n" of the 9 signs and symptoms) at this timepoint.
    b. Otherwise, if data was recorded for at least 6 of the 9 signs and symptoms and all meet the resolution condition described in (i) above, then the subject will be assigned code "S" (success).
    c. Otherwise, if fewer than 6 of the 9 signs and symptoms have data recorded then the subject will be assigned code “M” (missing).

The primary endpoint is defined as the time in hours from the time of randomization to the time of the first “S” in a sequence of 5 “SSSSS” for which there is no subsequent symptom recurrence or disease progression during the subjects’ remaining time on study. A maximum of one intermediate "M" is allowed within a sequence of at least 5 consecutive "S" values to also qualify as sustained resolution, i.e., "SMSSSS", "SSMSSS". "SSSMSS", and "SSSSMS" would each be counted as sustained resolution.

Note: Only timepoints after the time of randomization are considered when determining if the primary endpoint has been met.

After sustained resolution is achieved, **symptom recurrence** is defined as having three or more consecutive assessment times (corresponding to an approximately 24-hour period) where *two* or more of the nine sign and symptoms do not meet the resolution condition in (i). Any number of intermediate assessment times with M (missing) between the assessment

times with F_n (failure to resolve) where $n \geq 2$ symptoms or signs, does not prevent the subject from being classified as having experienced symptom recurrence.

A subject is defined to have had **disease progression** when they record "D" (disease progression) as defined in section 4.1(iii).

Note: A subject that has symptom recurrence and/or disease progression is still eligible to have the event for the primary endpoint later; if they subsequently have five consecutive assessments at which the signs and symptoms have resolved ("SSSSS"), but with no subsequent recurrence or disease progression during the subjects' remaining time on study.

4.2. KEY SECONDARY ENDPOINT

Note that at each of the twice-daily assessment times at which the subject is scheduled to take the SARS-CoV-2 antigen test, the results will be either Negative (N), Positive (P), Inconclusive (I), or Missing (M).

The key secondary endpoint is the **time to first of two consecutive negative SARS-CoV-2 antigen tests** (with a minimum time between tests of 6 hours) without subsequent virological rebound during the subject's remaining time on study. It is measured in hours from the time of randomization to the time of the first of two consecutive negative tests.

The following sequences will be counted as satisfying this condition of having "two consecutive negative SARS-CoV-2 antigen tests":

a) "NN" and the two tests are at least six hours apart.
b) More than two consecutive "N" values where the first and last are at least six hours apart.
c) "N" followed by at most three "M" or "I" values, followed by "N" where the two "N" values are at least six hours apart.

In the remainder of the SAP the use of "NN" will refer to any of cases (a)-(c).

Note: Only tests taking place after the time of randomization are considered when determining if the key secondary endpoint has been met.

Subsequent virological rebound is defined as having two or more positive tests out of three consecutive assessments. In addition to "PP", the following test result patterns, seen after one of (a) to (c) above, will be sufficient to define subsequent virological rebound:

i. "PPP"
ii. "PPN"
iii. "PNP"
iv. "NPP"

Note: If a “P” is followed by an “M” or "I" then the “P” will be carried forward so that this will also be counted as a subsequent virological rebound.

4.3. SECONDARY QUALITATIVE MEASURES

The following are secondary qualitative measures (each taking the values yes, no) recorded at the post-baseline clinic visits for COVID-related assessment:

- Loss of taste
- Loss of smell
- In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?
- In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?

4.4. SAFETY ENDPOINTS

The safety analysis will consider all TEAEs whether solicited (as part of the reactogenicity assessments including oropharyngeal assessment) or unsolicited.

In addition to TEAEs, the following safety endpoints will be assessed:

- Concomitant medications and therapies
- Vital signs
- Physical examination

Section 5. ANALYSIS POPULATIONS

The study uses three analysis populations which are defined below.

The treatment to which an individual is randomized should be determined using the answer to the question 'Randomization outcome' in the 'Randomization Assignment' CRF.

The treatment an individual actually received is to be determined by cross-referencing the 'Device ID' field in the 'RD-X19 Device Collection' with a list of which devices are active and which are sham.

5.1. FULL ANALYSIS SET (FAS)

The Full Analysis Set (FAS) will consist of the set of randomized subjects, excluding: (i) subjects who were mis-randomized; and (ii) subject IDs corresponding to study participants that were re-randomized under a different subject ID.

This population will be the primary analysis population for all efficacy endpoints. Subjects will be analyzed on the basis of the treatment to which they were randomized, regardless of what treatment they actually received.

5.2. SAFETY POPULATION

The safety population will consist of all randomized subjects who received any study treatment. Subjects will be analyzed on the basis of the treatment that they received.

This population will be the primary analysis population for all safety analyses.

5.3. PER PROTOCOL (PP) POPULATION

The Per Protocol (PP) Population will exclude from the FAS study subjects who experienced one or more of a pre-specified subset of major protocol deviations/violations, as well as subjects who did not meet certain pre-specified criteria concerning number of treatments received. The list of reasons for excluding subjects from the PP population is:

1. Subject received the wrong treatment
2. Subject not positive for COVID-19 based on qPCR
3. Did not satisfy Inclusion criteria #1, #3, and/or #4
4. Satisfied exclusion criteria #2 and/or #4
5. Number of treatments received was < 7
6. After randomization received one or more FDA-approved medications for COVID-19 treatment.

Subjects who did not satisfy any of #1-#4 above and received at least one treatment, but who only first satisfied #6 after visiting Urgent Care, visiting the Emergency Room, or after hospitalization will not be excluded from the PP population.

Section 6. GENERAL POINTS FOR STATISTICAL ANALYSIS

6.1. GENERAL METHODS

All statistical analyses as covered by this SAP will be performed using two different programming languages, for example, R version 3.4.1 or later [6], Python version 3.11 or later [7], or SAS® version 9.4 or later [8] as a diverse self-checking pair.

Summary statistics for continuous variables will be:

- Number of non-missing observations
- Mean and standard deviation
- Median
- First and third quartiles
- Minimum and maximum
- Number of missing observations

Categorical variables will be summarized as counts and percentages of appropriate total, with 'missing' as an additional category.

6.2. DECIMAL PLACES

- The mean and median, as well as the first and third quartiles for a set of values, will be presented to 1 more decimal place than the original values.
- Standard deviations and confidence interval limits will be presented to 2 more decimal places than the original values.
- The minimum and maximum will report the same number of decimal places as the original values.
- Percentages will be displayed with 1 decimal place. Percentages will not be presented when the count is zero, and 100% will be presented with no decimal place. Note that for categorical data, the number of missing observations will be included in the calculations.
- P-values will be displayed with 3 decimal places.

6.3. WITHDRAWALS AND MISSING DATA

A randomized subject will be taken as having withdrawn from the study if, with regards to the 'study exit' CRF, the question 'Did the subject successfully complete the study?' is answered 'no'.

A subject will be taken to have completed the study if the answer to the 'study exit' CRF question 'Did the subject successfully complete the study' is 'yes'.

See Section 4.1 for the handling of missing data for the primary endpoint.

See Section 4.2 for the handling of missing data for the key secondary endpoint.

Each of the baseline covariates included in the NPANCOVA method have rules to impute any missing values, and these are described in Section 8.2.1.3.

Incomplete values of 'date stopped smoking' will also be imputed. The rules are:

- Day is imputed as the 15th day of the given month if only day missing e.g. 'July 2000' becomes '15th July 2000'
- Day and month will be imputed as 1st July if day and month are missing e.g. '2000' becomes '1st July 2000'

Section 7. DISPOSITION AND BASELINE CHARACTERISTICS

The following variables will be summarised i.e. listed and/or tabulated by treatment group across the indicated population. Each section corresponds to a different table and/or listing and to either a single CRF or a combination of one or more CRFs. For details of the summaries, see the table shells and listings.

Categorical variables will be accompanied by possible values and '(Free text)' means the variable is categorical but the category is entered as free text by the study administrator. Otherwise, it will be assumed the variable is continuous. See Section 5: General Methods for the manner in which each variable type is summarised.

Note: These summaries will only be produced at the end of the study i.e. not the interim analysis.

7.1. INFORMED CONSENT

The following will be summarised over all screened subjects:

- Screening date (format of visit)
- Informed consent given (yes, no)
- Date of informed consent

7.2. SUBJECT DISPOSITION AND WITHDRAWAL

The following will be summarised in tabular form:

- Number of screened subjects
- Number of subjects who are screen failures
- Number of subjects Randomized
- Number of randomized subjects who completed the study
- Number of randomized subjects who did not complete the study, by reason (if more than one reason for a subject, count all reasons):
    - Screen failure
    - Progression to moderate or severe COVID-19
    - Pregnancy
    - (Serious) adverse event
    - Death
    - Protocol Deviation
    - Withdrawal by subject
    - Withdrawn at investigator's discretion
    - Termination of the study
    - Device deficiency
    - Lost to follow-up
    - Other

- Number of subjects in the FAS
- Reason(s) for subject exclusion from the FAS
    - Subject mis-randomized
    - Subject ID corresponds to study participant that was re-randomized under a different subject ID
- Number of subjects in Safety population
- Number of subjects in PP population
- Reason(s) for subject exclusion from the PP population (if more than one reason for a subject, include all reasons)
    - Received the wrong treatment
    - Subject not positive for COVID-19 based on qPCR
    - Did not satisfy Inclusion criterion #1
    - Did not satisfy Inclusion criterion #3
    - Did not satisfy Inclusion criterion #4
    - Satisfied exclusion criterion #2
    - Satisfied exclusion criterion #4
    - Number of treatments received was <7
    - After randomization received one or more FDA-approved medications for COVID-19 treatment.

All summaries will be provided by treatment group and percentages will be based on the number of subjects randomized to the treatment group, except for counts related to subjects screened or screen failures.

7.3. INCLUSION CRITERIA, EXCLUSION CRITERIA, PROTOCOL DEVIATIONS

Inclusion criteria not met, exclusion criteria met, and other Protocol Deviations will be summarised for all randomised subjects.

In addition, a listing will be produced including the following information for the FAS:

- Date of deviation
- Applicable study day
- Deviation category (inclusion/exclusion criteria, informed consent,…)
- Related to COVID-19 restrictions (Yes, no)
- Deviation pre-approved by sponsor (Yes, no)
- Type (major, minor)

7.4. E-DIARY TRAINING AND DEVICE

The following will be summarised over the FAS:

- E-diary training completed (yes, no)
    - If yes: date

- If no: reason

- RD-X19 device provided to the subject (yes, no)
    - If yes: date
    - If no: reason
- Device to which randomised
- Device returned at study end

Device to which randomized can be found in the question 'Randomization outcome' in the 'Randomization Assignment' CRF.

Device returned can be found in 'Device ID' field in the 'RD-X19 Device Collection' with a list of which devices are active and which are sham.

7.5. DEMOGRAPHIC DATA

The following will be summarised in tables and listings for the FAS:

- Age at time of consent (continuous variable)
- Age category at time of consent (40-49, 50-59, 60-64, ≥65)
- Sex (male, female, undifferentiated, unknown)
- Weight (kgs),
- Height (m)
- BMI (kg/m^2)
- BMI category (< 18.5 = 'underweight'; ≥18.5 to <25 = 'healthy weight'; ≥25 to <30 = 'overweight'; ≥ 30 to <40 = 'obese'; ≥ 40 = `morbidly obese`).
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported, unknown)
- Race (American Indian, Alaska Native, Asian, Black, African American, Native Hawaiian or Pacific Islander, White, Two or more races, Not reported, Unknown)

7.6. BASELINE COVID-19-RELATED INFORMATION AND OTHER BACKGROUND CHARACTERISTICS

The following variables will be summarised in tables for the FAS.

- Result of baseline SARS-Cov-2 antigen test (positive, negative, inconclusive)
- SARS-Cov-2 antigen test type (Flowflex, BinaxNOW)
- Result of flu A rapid antigen test (positive, negative, invalid)
- Result of flu B rapid antigen test (positive, negative, invalid)
- Randomization Stratum (age 40-49, Disease Severity Score < 1.25; age 40-49, Disease Severity Score ≥ 1.25; age ≥50, Disease Severity Score < 1.25; age ≥50, Disease Severity Score ≥ 1.25)
- Total baseline disease severity score (continuous variable)
- Total baseline disease severity score (<1.0, ≥1.0-<1.25, ≥1.25-<1.75, ≥1.75)
- Baseline individual self-assessed symptom scores:

- Cough (0,1,2,3)
- Sore throat (0,1,2,3)
- Nasal congestion (0,1,2,3)
- Headache (0,1,2,3)
- Chills or sweats (0,1,2,3)
- Myalgia (0,1,2,3)
- Fatigue (0,1,2,3)
- Nausea, with or without vomiting (0,1,2,3)

- Loss of taste (yes, no)
- Loss of smell (yes, no)
- Baseline oral temperature (continuous variable)
- Baseline oral temperature (<100.5, ≥100.5 °F)
- Baseline heart rate beats/min (continuous variable)
- Baseline heart rate (<70, ≥70-<80, ≥80-<90, ≥90)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Oxygen saturation at rest (%)
- Respiratory rate at rest (continuous variable)
- Respiratory rate at rest (<20, ≥20 breaths/min)
- Oxygen saturation from Dyspnea on exertion assessment (%)
- Respiratory rate from Dyspnea on exertion assessment (continuous variable)
- Respiratory rate ≥20 and Oxygen saturation <96% from Dyspnea on exertion assessment (yes, no)
- Hours at screening since onset of first COVID-19 sign or symptoms (continuous variable)
- Hours at screening since onset of first COVID-19 sign or symptoms (≤24, >24-≤48, >48-≤72, >72)
- Baseline Risk Factor Score (as defined in Section 8.2.1.3)
- Baseline Log10 Nasopharyngeal Viral Load category (Not Detected or Below LLOQ; Above ULOQ; Numerical value between LLOQ and ULOQ, missing)
- Baseline Log10 Nasopharyngeal Viral Load (summary statistics [copies/mL] for numerical value between LLOQ and ULOQ)
- Result of SARS-Cov-2 qPCR test (positive, negative). Note: Any sample with detectable SARS-CoV-2 RNA will be classified as a “positive” qPCR test result, even if the viral load is below the assay’s lower limit of quantitation or if the result is “inconclusive”. Any other result will be classified as a “negative” qPCR test result.
- SARS-Cov-2 variant identified by qPCR (frequency distribution)
- COVID-19 Vaccination status (yes, no)
- Number of COVID-19 vaccinations received (frequency distribution)
- Previous COVID-19 diagnosis via FDA-approved diagnostic test (yes, no)
- Significant risk of exposure to COVID-19 over the past two weeks (yes, no)
- Type of exposure (commercial flight, major sporting event, contact with someone with COVID-19, other) (use COVID-19 risk of exposure subform)

7.7. MEDICAL HISTORY

The following will be summarised in listings for the FAS, and categorical variables as well as all details on Smoking history will also be summarized in tables:

- History of substance abuse (never, current, former)
    - If current or former: years of substance abuse, specify substance, use in last month
    - If former: years since stopped
- Drinking history (never, current, former)
    - If current or former: years of drinking, units per day, history of alcohol intoxications (yes, no)
    - If former: years since stopped
- Smoking history (never, current, former)
    - If current or former: years of smoking (summary statistics), cigarettes per day (summary statistics)
    - If former: years since stopped (>0-≤2, >2-≤10, >10)
- History of asthma (yes, no)
    - If yes: start date, end date/ongoing
- History of vasomotor rhinitis (yes, no)
    - If yes: start date, end date/ongoing
- History of hypersensitivity or severe allergic reaction to sun exposure?
    - If yes: start date, end date/ongoing
- Frequent and recurring presence of oral diseases/conditions? (yes, no)
    - If yes: start date, end date/ongoing
- Other significant medical history

7.8. PREGNANCY TESTING

The following variables will be summarized in listing form for the FAS.

The following will be taken from the 'Pregnancy test' CRF:

- Is subject of childbearing potential (yes, no)

- If no: reason (post-menopausal, surgically sterile, other)
- If yes: was a pregnancy test performed (yes, no)
    - If yes: date of test, result (positive, negative, invalid)

7.9. BASELINE MEDICATIONS AND THERAPIES

The following will be summarised within tables for the FAS:

- Medications/vitamins/supplement/therapies taken in the 30 days prior to screening and not ongoing at time of screening (yes, no)
- Concomitant medications/vitamins/supplement/therapies ongoing at time of screening (yes, no)
- History of use of any FDA-authorized treatment for COVID-19? (yes, no)
- History of any systemic antiviral therapies? (yes, no)
- History of oral or parenteral corticosteroid use, including use of nasal or inhalable steroids? (yes, no)
- History of any chronic medical condition that has required adjustments to the type, dose or schedule of medical treatments? (yes, no)
- Requirement to use narcotic medication for analgesia? (yes, no)

Section 8. ANALYSIS OF STUDY ENDPOINTS

8.1. INTERIM ANALYSIS

A blinded sample size review will be carried out by an independent statistician based on the first 164 randomized subjects after the last of these subjects has reached the Day 14/ET visit.

The pooled proportion (p_{obs}) of subjects with an event for the primary endpoint (sustained resolution of COVID-19 signs and symptoms without subsequent symptom recurrence or disease progression) will be determined, and if this is less than 0.70 then, in order to obtain approximately 228 such events at the end of the study, the total number of randomized subjects will be increased to:

$$326 \times \frac{0.70}{p_{obs}}$$

(rounded up to the next multiple of two, due to the 1:1 active:sham randomization) subject to a cap of 380.

The number of randomized subjects will not be decreased, and no unblinded assessment of efficacy will be carried out at this time.

A table will be produced summarizing this analysis. It will include:

- The number of randomized subjects on which the analysis is based
- The pooled proportion of subjects with sustained COVID-19 resolution
- The new number of randomized subjects for the study
- The change (increase only) from the original number

No other listings or tables will be produced as part of the interim analysis. A copy of the data used to undertake the interim analysis will be kept and archived.

8.2. PRIMARY ENDPOINT

All analyses of the primary endpoint will be carried out only after implementing all data handling rules described in Section 4.1.

All primary analysis for this endpoint will be based on the FAS.

Event times and censoring status will be listed; the censoring status will additionally be tabulated. The following rules for event times and censoring will be implemented in the analysis of the primary endpoint:

I. Subjects that are hospitalized will be censored at 360 hours, which corresponds to the end of the time window for the day 14 visit. This rule takes precedence over all other rules.
II. A subject that records "SSSSS" i.e., five consecutive timepoints (corresponding to an approximately 48-hour period) at which the signs and symptoms have resolved who does not have any subsequent symptom recurrence or subsequent disease progression during the subject's remaining time on study, will have the event at the time of the first "S" in this sequence.
III. A subject not satisfying case (i) or (ii), who takes nirmatrelvir/ritonavir or molnupiravir after initiating study treatment will be censored at the time that they first took this antiviral medication.
IV. Subjects not satisfying case (i), (ii), or (iii) will be censored at the last time that they have e-diary data recorded.

Note: Subjects taking nirmatrelvir/ritonavir or molnupiravir after initiating study treatment must have recorded "SSSSS" (or equivalent) prior to starting this antiviral medication to be counted under case (ii), and if not then they will be counted under case (iii).

Note: The CRF only records the date that a concomitant medication is started, and does not record the time. Therefore, for subjects in case (iii) the time of censoring will be taken as midday. However, if any case (iii) subjects started the medication on the day of randomization then the censoring time will be the latter of midday or the time of randomization.

For all analysis, the covariates adjusted for/covariates in any models are included in a footnote to any related tables or figures.

Counts and percentages will also be provided in the tables reporting NPANCOVA analyses for subjects, which in the notation of Section 8.2, are in each of cases (i), (ii), (iii), and (iv).

8.2.1. NPANCOVA Analysis

Ties will be handled using Efron's method [9].

The primary endpoint is time-to-event in nature and will be analysed using the nonparametric randomization-based covariate adjustment method of Saville and Koch (2013) [10] which is expanded to handle stratified randomisation by Hussey et al (2016) [11]. They refer to this method as NPANCOVA, and this naming will be preserved here.

NPANCOVA avoids the assumption of proportional hazards for each of the covariates. It does rely on the assumption of proportional hazards for the treatment effect as obtained from an unadjusted Cox proportional hazards model (with a single term for treatment and no

covariates), but as is well known the p-value associated with this unadjusted estimate is comparable to the p-value obtained from the nonparametric log-rank test.

The method also does not make any assumptions about the relationship between the covariates and the outcome. The log hazard ratio can be viewed as a stratified population-averaged estimate.

Step One

The NPANCOVA method begins by fitting a stratified treatment-only Cox proportional hazards model. The model formula is:

$$\lambda(t;\ z_{hij}) = \lambda_{0h}(t) \times \exp(\beta z_{hij}) \quad (1)$$

Where $\lambda(t;\ z_{hij})$ is the hazard at time t for subject j in stratum h in treatment group i, where in this case $h \in \{1,2,3,4\}$, $i \in \{1,2\}$, and $j \in \{1,2,\dots,n_{hi}\}$, where n_{hi} is the number of randomized subjects in treatment group i in that stratum. $\lambda_{0h}(t)$ is the baseline hazard function for stratum h, and z_{hij} is the treatment group indicator for subject j in stratum h in treatment group i, which takes on a value 1 for the RD-X19 treatment group and 2 for the sham treatment group. In the next step, the Cox model from which DFBETA is obtained will have RD-X19 as the reference.

Step Two

The vector, ***r,*** of DFBETA residuals is then calculated from fitting model (1) to all FAS subjects.

The DFBETA residual r_{ijh} concerns subject j in stratum h in treatment group i, and is equal to the absolute change in the estimated log hazard ratio, $\hat{\beta}$, resulting from model (1) but with subject j removed from the data set. It can be interpreted as a measure of the subject's influence.

The DFBETA residuals for all subjects are obtained from the stratified, treatment only Cox proportional hazards model. Define:

$$\boldsymbol{r}_{hi} = \left(r_{hi1}, r_{hi2}, r_{hi3}, \dots, r_{hin_{hi}}\right)^T$$

as the vector of DFBETA residuals for subjects in stratum h in treatment group i.

We then concatenate all the $\boldsymbol{r}_{hi}$, resulting in a vector, $\boldsymbol{r}$, of length n, where n is the number of randomized subjects in the study. In this study, because we have four strata and two treatment groups, so $\boldsymbol{r}$ will be constructed as:

$$\boldsymbol{r} = \left(\boldsymbol{r}_{11}^{\boldsymbol{T}}, \boldsymbol{r}_{12}^{\boldsymbol{T}}, \boldsymbol{r}_{21}^{\boldsymbol{T}}, \boldsymbol{r}_{22}^{\boldsymbol{T}}, \boldsymbol{r}_{31}^{\boldsymbol{T}}, \boldsymbol{r}_{32}^{\boldsymbol{T}}, \boldsymbol{r}_{41}^{\boldsymbol{T}}, \boldsymbol{r}_{42}^{\boldsymbol{T}}\right)^{T}$$

Through the methods of Wei et al [12], as indicated by Saville & Koch (2013) [10] a robust estimate of the variance of $\hat{\boldsymbol{\beta}}$ (prior to adjusting for any covariates) is provided by the quantity $\boldsymbol{r}^{\boldsymbol{T}}\boldsymbol{r}$.

Step Three

The method requires within-strata randomisation with regards to treatment allocation. In the present case there are four strata, corresponding to the crossing of two binary covariates: age (40-49 or ≥ 50) and baseline disease severity score (< 1.25 or ≥ 1.25). These will be coded as follows:

Stratum subscript (h)	Stratum
1	40-49, < 1.25
2	40-49, ≥ 1.25
3	≥ 50, < 1.25
4	≥ 50, ≥ 1.25

Furthermore, 1 will refer to the RD-X19 treatment group and 2 the Sham treatment group. So, for example, those in the RD-X19 treatment group within stratum ≥ 50, < 1.25 will have subscript '31' i.e., subject $\boldsymbol{j}$ in this stratum will have covariate vector $\boldsymbol{x}_{31j}$; those in stratum 40-49, < 1.25 in the Sham treatment group will have subscript '12' i.e., subject $\boldsymbol{j}$ in this stratum will have covariate vector $\boldsymbol{x}_{12j}$.

NPANCOVA adjusts an initial estimate of the log hazard ratio (resulting from a treatment-only Cox proportional hazards model as in Step One) for covariates in a nonparametric manner. In this case, covariates are prognostic baseline covariates chosen to improve precision of the estimate of the log hazard ratio. Those covariates are:

- Baseline Log10 nasopharyngeal viral load
- Ethnicity
- Hours since onset of symptoms
- Baseline Risk Factor Score (BRFS).

Further details on the definitions and numerical values for these baseline covariates and imputation of their missing values is described in Section 8.2.1.3. These covariates will be indexed as follows:

Index	Covariate
1	Baseline Log10 nasopharyngeal viral load
2	Ethnicity

3	Hours since onset of symptoms
4	Baseline Risk Factor Score

So, letting $\boldsymbol{x}_{hij}$ be the $p \times 1$ vector of covariates (p is the number of covariates) for the jth individual in treatment group i from stratum h, in $\boldsymbol{x}_{hij}$ the first element will be their baseline Log10 nasopharyngeal viral load value, the second element will be their Ethnicity value, etc.

$X_{hi}^T = \left(\boldsymbol{x}_{hi1}, \boldsymbol{x}_{hi2,}, \boldsymbol{x}_{hi3}, \dots, \boldsymbol{x}_{hin_{hi,}}\right)$ is a $p \times n_{hi}$ matrix containing the covariate information for the subjects in stratum h in treatment group i.

The $p \times 1$ vector of covariate means in stratum h, treatment group i is given by:

$$\overline{\boldsymbol{x}}_{hi} = \frac{\sum_{j=1}^{n_{hi}} \boldsymbol{x}_{hij}}{n_{hi}}$$

and we define the $n_{hi} \times p$ matrix:

$$C_{hi} = k\left(X_{hi} - \mathbf{1}\overline{\boldsymbol{x}}_{hi}^T\right)$$

where $\mathbf{1}$ is a column of 1s (with the same number of rows as X_{hi}), meaning $\mathbf{1}\overline{\boldsymbol{x}}_{hi}^T$ is a matrix of the same dimension as X_{hi}, where:

$$k = \frac{n_{h1}n_{h2}}{n_h W\sqrt{n_{hi}(n_{hi}-1)}}$$

and

$$W = \sum_{h=1}^{4} \frac{n_{h1}n_{h2}}{n_h}$$

Where n_h is the number of subjects in stratum h and n_{h1} and n_{h2} are the numbers within stratum h in treatment groups 1 and 2, respectively.

The matrix $\boldsymbol{C}_{hi}$ can be interpreted as a scaled measure of the subject-wise deviations from the mean covariate values for stratum h in treatment group i.

An unbiased estimate for the covariance matrix of $\overline{\boldsymbol{x}}_{hi}$, the vector of covariate means for those in treatment group i in stratum h, is then given by:

$$V_{\overline{\boldsymbol{x}}_{hi}} = C_{hi}^T C_{hi}$$

Step Four

We then define:

$$\boldsymbol{f} = \left(\hat{\beta}, \overline{\boldsymbol{g}}^{\boldsymbol{T}}\right)^{T}$$

as a row vector of length 5. This is the concatenation of the estimate for β (a scalar) and $\overline{\boldsymbol{g}}$ (which has length 4), where $\overline{\boldsymbol{g}} = \overline{\boldsymbol{x}}_{\boldsymbol{1}} - \overline{\boldsymbol{x}}_{\boldsymbol{2}}$ is the (column) vector of weighted differences in covariate means between treatment groups, where

$$\overline{x_i} = \sum_{h=1}^{4} \frac{n_{h1} n_{h2} \overline{\boldsymbol{x}}_{hi}}{n_h W} .$$

A consistent estimate of $\boldsymbol{f}$'s covariance matrix is then given by:

$$V_f = \begin{bmatrix} \boldsymbol{r}^T \boldsymbol{r} & \sum_{h=1}^{4} (\boldsymbol{r}_{h1}^T C_{h1} - \boldsymbol{r}_{h2}^T C_{h2}) \\ \sum_{h=1}^{4} (C_{h1}^T \boldsymbol{r}_{h1} - C_{h2}^T \boldsymbol{r}_{h2}) & \sum_{h=1}^{4} \sum_{i=1}^{2} C_{hi}^T C_{hi} \end{bmatrix}$$

This is written more succinctly as:

$$V_f = \begin{bmatrix} v_{\hat{\beta}} & V_{\hat{\beta}\overline{\boldsymbol{g}}}^T \\ V_{\hat{\beta}\overline{\boldsymbol{g}}} & V_{\overline{\boldsymbol{g}}} \end{bmatrix}$$

As described in step 2 the quantity $\boldsymbol{r}^T \boldsymbol{r}$ $(= v_{\hat{\beta}})$ is a robust estimate of the variance of the estimator $\hat{\beta}$ (prior to adjusting for any covariates).

The quantity $V_{\hat{\beta}\overline{\boldsymbol{g}}}$ provides an estimate of the covariance matrix for $\hat{\beta}$ and $(\overline{\boldsymbol{x}}_{\boldsymbol{1}} - \overline{\boldsymbol{x}}_{\boldsymbol{2}})$.

The quantity $V_{\overline{\boldsymbol{g}}}$ provides an estimate of the covariance matrix for $(\overline{\boldsymbol{x}}_{\boldsymbol{1}} - \overline{\boldsymbol{x}}_{\boldsymbol{2}})$. This is an unbiased estimate under the assumption that the subjects are a simple random sample from a stratified population.

Step Five

A covariate-adjusted estimate of the log hazard ratio β – call it $\hat{b}$ – can then be obtained using weighted least squares methodology, by forcing the difference in means for the P covariates to zero, because under stratified randomization no differences between the stratification-adjusted means of the covariables are expected between the two treatment groups.

This translates to the following calculation for an estimate of b:

$$\hat{b} = \left(Z^T \left(V_f^T\right)^{-1} Z\right)^{-1} Z^T V_f^{-1} f \quad (2)$$

where $Z = \left(1, \mathbf{0}_p^T\right)^T$, $\mathbf{0}_p^T$ is a zero vector of length p, and, in terms of $\hat{\beta}$, is equivalent to:

$$\hat{b} = \hat{\beta} - V_{\hat{\beta},\bar{\boldsymbol{g}}}^T V_{\bar{\boldsymbol{g}}}^{-1} \bar{\boldsymbol{g}}$$

A consistent estimator for the variance of b is:

$$\begin{aligned} v_b &= v_{\hat{\beta}} - V_{\hat{\beta},\bar{\boldsymbol{g}}}^T V_{\bar{\boldsymbol{g}}}^{-1} V_{\hat{\beta},\bar{\boldsymbol{g}}} \\ &= \left(Z^T V_f^{-1} Z\right)^{-1} \end{aligned} \quad (3)$$

The reportable values are the hazard ratio estimate, $e^{\hat{b}}$, along with its p-value and 95% confidence interval and $\sqrt{v_b}$, the standard error of the estimator for the log hazard ratio.

8.2.1.1. HYPOTHESIS TESTING

The test statistic will be

$$Z = \frac{\hat{b},}{\sqrt{v_b}} \quad (4)$$

which under H_0 has an asymptotic $N(0,1)$ distribution.

A test will be carried out at the 5% two-sided significance level with the following hypotheses:

$$H_0: \beta = 0$$

$$H_1: \beta \neq 0$$

and the p-value reported.

Here only a p-value favoring the RD-X19 treatment group will be flagged as statistically significant. This p-value corresponds to the primary analysis of the primary endpoint.

8.2.1.2. CONFIDENCE INTERVAL

Under the assumption of a normal distribution for the log hazard ratio estimate, $\hat{b}$, a 95% confidence interval for the log hazard ratio will be calculated with limits given by:

$$\hat{b} \pm \Phi(0.975) \times \sqrt{v_b} \quad (5)$$

where $\Phi(.)$ is the inverse cumulative density function for the standard normal distribution. A confidence interval for the hazard ratio will be generated by exponentiation of the limits of this confidence interval.

This confidence interval for the hazard ratio is a reportable value.

8.2.1.3. Definitions of Baseline Covariates and Imputation of Missing Values for these Covariates

Nasopharyngeal viral load numerical values (copies/mL) are recorded at baseline. For the viral load quantitation assay, the specified lower limit of quantification (LLOQ) and limit of detection (LOD) are both 5.0 x 10^2 copies/mL (which is 2.6990 on the Log10 scale) and the upper limit of quantification (ULOQ) is 5.0 x 10^8 copies/mL (which is 8.6990 on the Log10 scale). Most subjects are expected to have a numerical value between LLOQ and ULOQ. Although the specified LOD and LLOQ for this specific PCR assay are equal (5.0 x 10^2 copies/mL), it is possible for a sample to have result “Detected, but below the LLOQ” if the amount of viral RNA in the sample is less than the LOD (the minimum concentration at which viral RNA can be reliably detected). Subjects with a recorded value of "Not detected" (which corresponds to a value below the LOD) or “Detected, but below the LLOQ” will be assigned a value equal to half the LLOQ, i.e., 2.5 x 10^2 copies/mL (which is 2.3979 on the Log10 scale). Similarly, any subjects with "Detected" and noted to be "above ULOQ” will be assigned a value equal to twice the ULOQ, i.e., 1.0 x 10^9 copies/mL (which is 9.0 on the Log10 scale).

The first covariate is Baseline Log10 nasopharyngeal viral load numerical values and so all numerical values will be in the range 2.3979 to 9.0. If at baseline the assay is not carried out, then prior to imputation the value of nasopharyngeal viral load will be set to missing.

Ethnicity is recorded at baseline as "Hispanic or Latino", "Non-Hispanic or Latino", "Not Reported", or "Unknown". The Ethnicity covariate will assign a value 0 to "Hispanic or Latino" and assign a value 1 to "Non-Hispanic or Latino". For other categories (prior to imputation) the numerical value for the Ethnicity covariate will be set to missing.

Hours since onset of symptoms is determined by subtracting the time/date of onset of symptoms from the time/date of screening. If either date is missing then prior to imputation the numerical value for the Hours since onset of symptoms covariate will be set to missing.

Baseline Risk Factor Score (BRFS) is a numerical score that considers 12 individual risk factors for progression. Each individual risk factor contributes 0 to the BRFS if not present and contributes a value of either 1 or 2 (as specified below) if the individual risk factor is present at baseline (but each medical history risk factor will contribute zero if the condition is not ongoing at baseline).

The following factors if present at baseline will contribute 1 to the BRFS: Age ≥65, Chronic Liver or Kidney Disease, Asthma, COPD, Cystic Fibrosis, Diabetes (type I or type II), Heart Disease, Hypertension, Immune Deficiency (including HIV), Cerebrovascular Disease (Stroke). For Overweight/Obesity, Overweight (BMI ≥25.0 to <30) will contribute a score of 1 and Obesity (BMI ≥30) will contribute a score of 2. For Smoking Status: (i) a Current Smoker will contribute a score of 2; (ii) a Former Smoker who stopped smoking ≤2 years ago will also contribute a score of 2; (iii) a Former Smoker who stopped smoking >2 but ≤10 years ago will contribute a score of 1; and (iv) a Former Smoker who stopped smoking >10 years ago will contribute a score of 0.

The BRFS covariate will be treated as a continuous variable, but the total score for an individual subject will be capped at $BRFS_{CAP}$ in order to avoid the undue influence in the NPANCOVA analysis of a few subjects with a very high score. The value of $BRFS_{CAP}$ will be set at 6 provided that the proportion of subjects with BRFS ≥ 6 is no more than 0.10. If not, then successively higher integer values for $BRFS_{CAP}$ will be considered until the proportion of subjects with BRFS ≥ $BRFS_{CAP}$ is no more than 0.10.

Note: At baseline the CRF captures specifically Age, BMI, Smoking status, and History of Asthma (with a field for whether or not it is ongoing). The CRF also captures all other medical History conditions/disorders as a text field and whether or not the subject separately for each of the eight specific factors (Chronic Liver or Kidney Disease, COPD, Cystic Fibrosis, Diabetes [type I or type II], Heart Disease, Hypertension, Immune Deficiency (including HIV), Cerebrovascular Disease [Stroke]) has the condition/disorder will be determined by manual review (prior to unblinding) of a list of those conditions/disorders that are ongoing at baseline.

Note: Only if the Medical History page is completely missing for a subject will the Baseline Risk Factor Score be considered (prior to imputation) to be missing.

Missing data for each of the covariates will be imputed as follows: For a given covariate the mean value of the non-missing values (for both treatment groups combined) in each of the 4 strata will be determined. Then subjects in stratum *h* with missing values for the covariate will be replaced by this mean of the non-missing values from stratum *h*.

8.2.1.4 DEGREE OF IMBALANCE AMONG THE COVARIATES

The (scalar) quantity Q_0 is determined to evaluate the extent of the random imbalances between the treatment groups and is defined by:

$$Q_0 = (\boldsymbol{f} - \boldsymbol{Z}b)^T V_f^{-1} (\boldsymbol{f} - \boldsymbol{Z}b)$$

It has an approximate X^2 distribution with 4 degrees of freedom. The value of Q_0 will be calculated, compared to the appropriate X^2 distribution, and a p-value calculated.

Note: The criterion is not a test for validity of NPANCOVA, but due to the stratified randomization requirement of the methodology small p-values for Q_0 should just be interpreted as a chance finding.

8.2.2. Kaplan-Meier Analysis

This analysis will be carried out on the FAS population. The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The plot will show the number of subjects at risk on the time axis, and the y-axis will indicate the success probability.

The median survival time will also be estimated for each treatment group (these medians will also be superimposed on the plot), together with its 95% CI using the Brookmeyer & Crowley method [13] (using the "log-log" transformation option). Estimates of the 25th and 75th percentiles and the median will be derived, along with their corresponding 95% CIs, and reported in a table.

8.2.3. Cox Proportional Hazards (PH) Analysis

A secondary analysis will be carried out on the FAS for the primary endpoint based on a stratified Cox PH model [14], using Efron's method for handling ties [9]. As for the primary analysis the Cox PH model will have RD-X19 as the reference. This analysis will use the same strata as the primary analysis. The same covariates for which the NPANCOVA analysis adjusted will also be incorporated into the Cox PH model (as covariates).

Only the (conditional) hazard ratio and its 95% confidence interval will be reported, along with its associated p-value. These quantities will be reported on the identity scale, i.e. they will be exponentiated before reporting. The covariates adjusted for will be specified in the table as a footnote.

8.2.4. Supportive Analysis

NPANCOVA, Kaplan-Meier and Cox PH supportive analyses of the primary endpoint will be carried out for the PP population.

8.2.5. Further Secondary and Sensitivity Analyses

A secondary analysis based on NPANCOVA will be carried out for the primary endpoint excluding the FAS subjects that were qPCR negative at baseline.

A sensitivity analysis based on NPANCOVA in the FAS will be carried out for the primary endpoint in which the following rules for event times and censoring will be implemented:

I. Subjects that are hospitalized, who progress to more severe forms of COVID-19, or who require therapy with an FDA-authorized COVID-19 treatment will be censored at 360 hours (which corresponds to the end of the time window for the day 14 visit). This rule takes precedence over all other rules.
II. A subject that records "SSSSS" i.e., five consecutive timepoints (corresponding to an approximately 48-hour period) at which the signs and symptoms have resolved who does not have any subsequent symptom recurrence or subsequent disease progression during the subject's remaining time on study, will have the event at the time of the first "S" in this sequence.
III. Subjects not satisfying case (i) or (ii) will be censored at the last time that they have e-diary data recorded.

Counts and percentages will be provided for subjects in each of cases (I), (II), and (III), as defined above. In addition, counts and percentages will be provided separately for subjects hospitalized, subjects who progress to more severe forms of COVID-19, and subjects who require therapy with an FDA-authorized COVID-19 treatment.

8.2.6. Subgroup Analyses

For the primary endpoint in the FAS an unstratified Cox PH model with a single term for treatment will be used to derive the hazard ratio and its 95% confidence interval for each of the following subgroups:

1. Region (West, South-East, North-East/Mid-West)
2. Hours at screening since onset of first COVID-19 sign or symptoms (≤24, >24-≤48, >48-≤72)
3. Previous COVID-19 diagnosis via FDA-approved diagnostic test (yes, no)
4. Prior COVID-19 vaccination (yes, no)
5. SARS-Cov-2 rapid antigen test type (Flowflex, BinaxNOW)
6. Age category (40-49, ≥50)
7. Sex (male, female)
8. Race (White, Black/African American, Other races combined)
9. Ethnicity (Hispanic or Latino, not Hispanic or Latino)
10. Total baseline disease severity score (<1.25, ≥1.25)
11. Baseline Log10 Nasopharyngeal Viral Load (≤median value, > median value)
12. Baseline Risk Factor Score (0-2, ≥3)

The study is powered on the basis of the overall treatment effect and is not designed to have high power for separate subgroup analyses.

The regions are defined as follows: (a) West consists of sites in Arizona, California, Nebraska, Nevada, Texas, Utah; (b) South-East consists of sites in Florida, Georgia, Louisiana, Mississippi, North Carolina, Tennessee; and (c) North-East/Mid-West consists of sites in Iowa, Illinois, Kentucky, Massachusetts, Maryland, Michigan, Missouri, New York, and Ohio).

For the subgroup analysis by race subjects with two or more races recorded will be included in the category "Other races combined", except for subjects reporting two races of "Black" and "African American" who will be included in the "Black/African American" category.

For the subgroup analysis by Baseline Log10 Nasopharyngeal Viral Load, the data will first be transformed as described in the first paragraph of Section 8.2.1.3, so that all non-missing values will be in the range 2.3979 to 9.0.

For the above subgroup analyses the following categories (all of which are expected to have very few if any subjects) will not be included: unknown, inconclusive, missing, not reported, undifferentiated (for gender only), and >72 hours (for hours since symptom onset only).

8.2.7. EXPLORATORY ANALYSES

Exploratory analyses of sign or symptom resolution by type of sign or symptom will be carried out as follows:

For each FAS subject separately for each symptom that is moderate or greater at baseline, the time to the first of five consecutive timepoints at which that symptom is resolved (to become mild or not present) will be determined. If this has not occurred, then the subject for this symptom will be censored at the last time that they have e-diary data recorded.

Similarly, for each FAS subject that has fever (temperature ≥ 100.5 °F) at baseline, the time to the first of five consecutive timepoints at which that sign is resolved (to become < 100.5 °F) will be determined. If this has not occurred, then the subject for this sign will be censored at the last time that they have e-diary data recorded.

For each treatment group Kaplan-Meier estimates of the median time to initial symptom resolution, together with its 95% CI, will be derived separately for each sign or symptom. For each treatment group baseline counts and percentages will also be provided separately for each sign or symptom.

8.3. KEY SECONDARY ENDPOINT

All analyses of the key secondary endpoint will be carried out only after implementing all data handling rules described in Section 4.2.

8.3.1. RULES FOR EVENT TIMES AND CENSORING

The following rules for event times and censoring will be implemented in the analysis of the key secondary endpoint:

i. Subjects that are hospitalized, who progress to more severe forms of COVID-19 or who require therapy with an FDA-authorized COVID-19 treatment will be censored at 360 hours (which corresponds to the end of the time window for the Day 14 visit). This rule takes precedence over all other rules.
ii. A subject that records "NN" based on two tests at least six hours apart without subsequent rebound during the subject's remaining time on study will have the event at the time of the first "N" in this sequence, and
iii. Subjects not satisfying case (i) or (ii) will be censored at the time of their last self-assessment /diagnostic test.

Note: Case (iii) subjects with no SARS-CoV-2 antigen tests after randomization will be censored at time zero.

The event times and censoring status will be listed.

8.3.2. ANALYSIS

The analysis of the key secondary endpoint will be based on the FAS and the same as that for the primary endpoint (primary: NPANCOVA, secondary: Kaplan-Meier and Cox PH analyses), using the same method for handling ties, the same stratification factors, and with the same pre-specified prognostic baseline covariates as included in the primary analysis of the primary endpoint. Counts and percentages will be provided in the tables reporting NPANCOVA analyses for subjects in each of cases (i), (ii), and (iii), as defined in Section 8.3.1. In addition, counts and percentages will be provided separately for subjects hospitalized, subjects who progress to more severe forms of COVID-19, and subjects who require therapy with an FDA-authorized COVID-19 treatment.

Supportive analyses (NPANCOVA, Kaplan-Meier, and Cox PH analyses) of the key secondary endpoint will be carried out for the PP population. A secondary analysis based on NPANCOVA will be carried out for the key secondary endpoint excluding the FAS subjects that were qPCR negative at baseline. Subgroup analyses based on the FAS will also be provided for the key secondary endpoint by SARS-Cov-2 rapid antigen test type (Flowflex, BinaxNOW). This subgroup analysis will be based on an unstratified Cox PH model with a single term for

treatment from which the hazard ratio and its 95% confidence interval will be derived for each of the two categories of this subgroup.

8.3.3 Multiplicity Adjustment

The key secondary endpoint will only be formally tested if statistical significance has been obtained for the primary endpoint.

This step-down procedure ensures that there will be strong control of the experiment-wise type 1 error across the primary endpoint and the key secondary endpoint.

If the primary endpoint is found to be non-significant, the key secondary endpoint will still be analysed but a footnote will be added to all related tables for the key secondary endpoint stating that p-values and confidence intervals are to be viewed as descriptive.

8.4. Secondary Qualitative Measures

The COVID-19 related assessments, which are secondary qualitative measures, will be summarised for the Day 5, 8 and 14 Visits.

The following will be tabulated for the FAS:

- Loss of taste (yes/no), both overall and separately among subjects who recorded loss of taste at baseline
- Loss of smell (yes/no), both overall and separately among subjects who recorded loss of smell at baseline
- In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)? (yes/no)
- In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)? (yes/no)

A listing will also be provided for the COVID-19 related assessments.

8.5. SAFETY ENDPOINTS

The safety endpoints will be summarised (i.e. listed and/or tabulated) for the safety population.

8.5.1. EXPOSURE

'Exposure' is defined as the number of COVID-19 treatments (out of the 14 scheduled) that an individual undergoes during their time on the study.

This information will be tabulated as both a continuous and categorical variable (categories: 0,1,2,3,4,5,6,7,8,9,10,11,12,13,14).

A listing will also be produced which provides information on the Day number and time that each treatment is taken, with a flag to indicate if the treatment was given in Clinic, a yes/no variable for whether the subject discontinued treatment due to an TEAE/TESAE, the coded TEAE term for subjects with Yes (for discontinued treatment due to an TEAE or TESAE), the day number that treatment was discontinued (where applicable), a yes/no variable for whether the subject discontinued the study, the reason (that trial subject discontinued the study) for subjects with Yes, the day number that the subject discontinued the study.

8.5.2. CONCOMITANT MEDICATIONS AND THERAPIES

Concomitant medications and therapies will be defined as medications and therapies begun after first treatment, and they will be summarised for the safety population.

Note: Medication/therapy detailed information comes from associated 'Medication' and 'Therapy' CRFs. WHODrug coding information comes from an associated 'WHOdrug coding' CRF.

The following information will be listed:

- Was the medication/therapy prescribed during the study (yes, no)
- Category (head, ears, eyes, nose, throat, mouth, cardiovascular system, lungs, pancreas, kidney, urological system, nervous system, blood, lymph nodes, endocrine system, musculoskeletal system, skin, genital/reproductive tract, allergies, cancer, immunodeficiency, psychiatric illness, substance abuse, autoimmune disease, other)
- Start date/Stop date (stop date can be 'ongoing')
- Reason for use (COVID-19 symptoms, chronic disease/medical history, adverse even, other)
- Indication (if therapy only)
- Dose
- Dose unit (capsule, drop, …)
- Dose form (aerosol, capsule, …)
- Frequency (once, twice weekly, …)
- Generic drug name and drug code
- WHOdrug product name
- Preferred name

- ATC text
- Start date/End date (End date can be 'ongoing')

In addition, the same listing will be produced but restricted to concomitant medications that are given for COVID-19 related symptoms.

A table will be produced listing counts of the different types of concomitant medications/therapies (only those taken after initiating treatment) in each of the ATC highest level classification groups along with whether or not the individual medication was prescribed during the study (yes/no).

In addition, the same table will be produced but restricting those concomitant medications to those given for COVID-19 related symptoms.

Since the CRF does not identify which medications and therapies were given for COVID-19 related symptoms, the sponsor will provide Quantics with a separate data set with a flag indicating which medications and therapies to which this applies.

8.5.3. Adverse Events

All adverse event (AE) tables will be produced for the Safety population, and will be presented by treatment group. The AE incidence tables will all be based on treatment-emergent adverse events (TEAEs), but all listing-type tables and the AE data listing will also include non-treatment-emergent AEs. A TEAE is defined to be an AE which starts after initiation of treatment, or a medical condition which was present prior to initiating treatment but which increases in severity after starting treatment. TEAEs will be captured and identified by the investigator who will assess the increase in severity part of the TEAE definition by comparing post-baseline Medical History/Physical Examination with baseline Medical History/Physical Examination. The only possible non-TEAEs recorded could be those AEs experienced between signing the ICF and the time of the first treatment, but as this time period is very short it is expected that there will be very few if any AEs that are not TEAEs. All AEs will be coded using MedDRA version 23.0 or higher.

The following 12 incidence tables will be produced for TEAEs which for #2-#8 will be sorted by system organ class (SOC) and preferred term (PT):

1. Overall TEAE summary table (with counts for #2-#12)
2. TEAE incidence table
3. Treatment-emergent SAE (TESAE) incidence table (including a separate count for any deaths)
4. TEAE incidence table by severity
5. Device-Related TEAE (DR-TEAE) incidence table
6. DR-TEAE incidence table by severity
7. Anticipated DR-TEAE incidence table
8. Unanticipated DR-TEAE incidence table overall and by severity
9. Solicited TEAEs incidence table overall and by severity
10. Solicited DR-TEAEs incidence table overall and by severity
11. TEAEs leading to discontinuation of treatment - incidence table

12. TEAEs leading to discontinuation from the study - incidence table

For subjects experiencing the TEAE more than once only the most severe will be counted in the incidence tables.

Anticipated DR-TEAEs are those described in Protocol Section 5.2.1, and are anticipated provided that all of the following applies: (i) occurred post-treatment with severity of mild; (ii) did not lead to discontinuation of treatment; and (iii) did not lead to discontinuation from the study. Anticipated DR-TEAEs will be identified by a pre-specified list of MedDRA coded terms or a listing will be provided to Quantics with an identifying flag for any AEs that correspond to an anticipated DR-TEAE.

Unanticipated DR-TEAEs include those TEAEs reported as device-related and which are not described in Protocol Section 5.2.1. In addition, those TEAEs described in Protocol Section 5.2.1 for which any of the following occurs will also be classified as unanticipated: (i) occurred post-treatment with severity of moderate or severe; (ii) led to discontinuation of treatment; or (iii) led to discontinuation from the study.

Solicited TEAEs are those collected by direct questioning of study subjects and are recorded on the CRF pages for Reactogenicity assessment including oropharyngeal assessment. [Unsolicited TEAEs are those spontaneously reported by the subject and/or in response to an open question from study staff or revealed by observation, physical examination, or other diagnostic procedure.] The incidence tables for solicited TEAEs, as derived from the Reactogenicity CRF page, will summarize:

- Clinical judgement (normal, abnormal not due to device, abnormal due to device)
- Pain (absent, present [overall and separate counts for mild, moderate, severe])
- Erythema at the illumination site (absent, present [overall and separate counts for mild, moderate, severe])
- Edema/induration at the illumination site (absent, present [overall and separate counts for mild, moderate, severe])
- Any other pain, redness, swelling or lesion of the oral mucosa (absent, present [overall and separate counts for mild, moderate, severe])

Subjects experiencing the individual solicited TEAE more than once will be counted in the incidence tables under the most severe category. For "Clinical judgement" here also only the most severe will be counted (where "abnormal due to device" is regarded as the "most severe" for this purpose).

The following listing-type tables will be produced:

13. Listing-type table of SAEs
14. Listing-type table of Device-Related SAEs

15. Listing of all hospitalizations including for COVID-19-related symptoms as determined by Hospitalization being recorded as an action taken in the AE CRF.
16. Listing-type table of AEs occurring while patient was hospitalized
17. Listing-type table of Deaths
18. Listing-type table of AEs leading to treatment discontinuation

In #13-#16 and #18 non-TEAEs, if any, will be flagged.

A full data listing will also be produced for reactogenicity assessment and oropharyngeal assessment including all information from these CRF pages at the Day 1, Day 5, Day 8, and Day 14/Early Termination study visits. Similarly, a full data listing will be produced based on information collected on the AE page, where non-TEAEs, if any, will be flagged.

8.5.4. Vital Signs

As the Baseline, Day 5, Day 8, and Day 14 Clinic Visits vital signs are collected as a value and then classified on the basis of the following two questions:

- Value out of range (yes, no)
- Clinically significant (yes, no)

Some vital signs are scheduled to be collected three times at each timepoint for which an average value is then calculated. If for these vital signs less than three assessments are performed then the average of the values collected is used instead.

Variables tabulated (over the safety population) by visit are:

- Oxygen saturation (%)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart rate (beats/min)
- Oral temperature (°F)
- Respiratory rate (breaths/min)

Note: Oxygen saturation and oral temperature are scheduled to be recorded twice daily for Days 1-14 and the tabulated values for these two vital signs will include (average) values recorded in their diary entries as well as the values recorded at the Clinic Visits.

8.5.5. Physical Examination

The following information will be listed and frequencies will be tabulated over the safety population. This is performed only at baseline, the day 14 visit, and Early Termination, and as such will only be summarised at those timepoints.

Unless otherwise indicated, the classes are: normal, abnormalities but no clinical significance, abnormal with clinical significance. Note: If 'abnormal with clinical significance' a free-text explanation is given.

- Assessment performed (yes, no)
- Skin
- Head
- Ears
- Eyes
- Nose
- Throat
- Neck
- Lungs
- Heart
- Liver
- Spleen
- Abdomen
- Extremities
- Lymph nodes, axillary and cervical
- Nervous system

8.5.6. Device Deficiency

A listing-type table will be produced covering all instances of "device deficiency" as reported by the site on the CRF. Any devices reported at the site as being deficient will, after return to the sponsor, undergo an engineering assessment. In this listing-type table a field will be included which signifies whether (yes, no) this engineering assessment concluded that the device was actually deficient.

The sponsor will provide these engineering assessments to Quantics after study completion as a separate data set.

Section 9. LIST OF TABLES, LISTINGS AND FIGURES

A complete set of shell tables listing figures is attached as an additional document.

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