Protocol #: MHICC-2020-003

A phase 2, randomized, double-blind, placebo-controlled study of hesperidin therapy on COVID-19 symptoms:
The Hesperidin Coronavirus study (Hesperidin)

NCT #: NCT04715932

Statistical Analysis Plan (SAP)

Version 29-Apr-2021

Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute

MHICC

STATISTICAL ANALYSIS PLAN

Protocol number: MHICC-2020-003

A phase 2, randomized, double-blind, placebo-controlled study of hesperidin therapy on COVID-19 symptoms: The Hesperidin Coronavirus study

Hesperidin

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Signature Approval Page

By signing below, I indicate that I have reviewed the Statistical Analysis Plan in its entirety and approve its contents.

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Revision History

Version	Date (DD-MMM-YYYY)	Author	Summary of Changes
Final	29-APR-2021	Camille Rosa	Initial version

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LIST OF ABBREVIATIONS

ACE2	Angiotensin Converting Enzyme 2
AE	Adverse Event
eCRF	Electronic Case Report Form
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
e-Consent	electronic Consent
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ITT	Intent To Treat
IUD	Intrauterine device
IRB	Institutional Review Board
LPS	Lipopolysaccharides
MHICC	Montreal Health Innovations Coordinating Center
PCR	Polymerase Chain Reaction
qPCR	quantitative Polymerase Chain Reaction
PP	Per Protocol
PO (po)	Per os
PRN	pro re nata (as necessary)
SAE	Serious Adverse Event
SOPs	Standard operating procedures
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TESS	Treatment-Emergent Signs and Symptoms
WMA	World Medical Association

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the final analysis of Montreal Heart Institute protocol MHICC-2020-003. This plan also provides a description of the tables, figures and listings that will be included in the final statistical report. It is based on the protocol dated 17FEV2021 and on the annotated case report form (CRF) version 2.0. In case of differences in terms of descriptions or explanations between the SAP and the clinical protocol, the SAP will supersede the protocol. Any deviation to this SAP would be reported in the statistical report.

2 STUDY DESCRIPTION

2.1 Study Design

This will be a randomized, double-blind, placebo-controlled study. The study will include subjects from Quebec diagnosed with COVID-19 infections. Following informed consent, 216 subjects meeting all inclusion and no exclusion criteria will be randomized to receive either hesperidin (1000 mg q.d.) or placebo (1:1 allocation ratio) for 14 days. Investigational drug will be delivered to the patients' homes. In addition, patients will be provided with an oral electronic thermometer as well as a daily symptoms diary (see Appendix A). Follow-up phone assessments will occur after 3 7, 10, and 14 days following randomization for evaluation of the occurrence of any trial endpoints or other adverse events. Electronic CRF (eCRF) will be completed by the research personnel over the phone with the patients.

The schedule of visits for this study is outlined in Appendix B. However, a patient may be evaluated at any time for safety concerns.

2.2 Study Objectives

The primary objective of the study is to determine the effect of hesperidin therapy on the presence of selected COVID-19 symptoms (fever, cough, shortness of breath or anosmia) at 3, 7, 10, and 14 days following randomization.

The secondary objectives are:

1- To determine the effect of hesperidin therapy on the mean number of COVID-19 symptoms at 3, 7, 10, and 14 days following randomization.
2- To determine the effect of hesperidin therapy on the duration of COVID-19 symptoms.
3- To determine the effect of hesperidin therapy on the presence of each individual COVID-19 symptoms at 3, 7, 10, and 14 days following randomization.

The exploratory objectives are:

1- To evaluate the effect of hesperidin therapy on the presence of each individual COVID-19 symptoms on a daily basis based on a patient symptoms' diary.
2- To evaluate the effect of hesperidin therapy on COVID-19-related hospitalization, mechanical ventilation and death in the 14 days following randomization.

3 Datasets Analyzed

Subjects who were not eligible for randomization but who have been erroneously randomized into the study will be excluded from all datasets analyzed, if they did not take study medication. In this study, pregnancy tests are shipped with the medication at randomization. In case of positive pregnancy test, women will not be eligible and will also be excluded from all datasets analyzed, if they did not take study medication.

3.1 Intent-To-Treat (ITT) Population

All patients randomized that have been delivered study medications will be included in the ITT population (i.e. subjects having a randomization number on the Randomization Form of the electronic case report form (eCRF)), excluding randomized women whose pregnancy test is positive. In the ITT population, subjects allocated to a treatment group by randomization will be followed up, assessed and analyzed as members of that group irrespective of their compliance to the planned course of treatment. ITT population will be approved by the sponsor prior to database lock.

3.2 Safety Population

All patients who took at least one dose of study medication will be included in the safety population. Patients will be assigned according to the true treatment received for analysis purposes. If a patient receives hesperidin at randomization or as supplemental bottle, the true treatment received will be imputed as hesperidin. The subjects of the safety population will be identified using the variable MEDIC of the Study Medication Administration Form of the eCRF. If a woman with a positive pregnancy test took at least one dose of study medication even it is not recommended, she will be included in the safety population. The same will apply if the unlikely case of a subject erroneously randomized who took at least one dose of study medication. Safety population will be approved by the sponsor prior to database lock.

4 EFFICACY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary endpoint will be the proportion of subjects with any of the following COVID-19 symptoms: fever, cough, shortness of breath or anosmia, at day 3, 7, 10 and 14 of the patient's symptoms diary. Presence of these symptoms (Yes/No) will be identified using the Covid-19 Symptoms Form of the eCRF (variables COUGH, FEVER [considered a symptom if greater than 38^{o}], SBREATH and ANOS respectively) at DAY 3, DAY 7, DAY 10 and DAY 14.

4.2 Secondary Efficacy Endpoints

- Mean number of COVID-19 symptoms (range 0 – 13) at day 3, 7, 10 and 14 of the patient symptoms' diary. This endpoint will be derived using the Covid-19 Symptoms Form of the eCRF at

DAY 3, DAY 7, DAY 10 and DAY 14. For each subject, the number of symptoms reported as 'Yes' will be calculated, adding one if the symptom "Fever" is greater than 38°.

- Duration of COVID-19 symptoms, defined as the number of days between randomization and complete disappearance of symptoms. More specifically, duration of COVID-19 symptoms will be taken as day of complete disappearance (because randomization is DAY 0). Subjects who will still have at least one symptom at their last assessment will be censored at the day of this last assessment.

  To determine day of complete disappearance of symptoms, all symptom assessments from the patient's diary will be sorted by day (variable DAYPARM). At each time point, the assessment will be categorized as complete disappearance of symptoms (if number of symptoms = 0) or no complete disappearance of symptoms (if number of symptoms > 0).

  - ✓ If there is complete disappearance of symptoms at Day 14 (or last assessment), day of complete disappearance is the first day when complete disappearance occurred with no relapse.
  - ✓ If there is no complete disappearance of symptoms at Day 14 (or last assessment), the day of this last assessment will be the censoring day.

  It should also be noted that subjects who do not complete the study will be classified as still having symptoms (i.e. no complete disappearance) REGARDLESS if symptoms disappeared earlier. Date of censoring will be the date of study discontinuation.

- For each of the 13 COVID-19 symptoms listed in the appendix, proportion of subjects with the symptom at day 3, 7, 10 and 14 of the patient symptoms' diary. Presence of these symptoms (Yes/No) will be identified using the Covid-19 Symptoms Form of the eCRF (variables COUGH, FEVER [considered a symptom if greater than 38°], FEVERISH, STHROAT, …, ANOS) at DAY 3, DAY 7, DAY 10 and DAY 14.

4.3 Tertiary (or Exploratory) Efficacy Endpoints

- For each of the 13 COVID-19 symptoms listed in the appendix, proportion of subjects with the symptom on a daily basis based on patient's diary. Presence of these symptoms (Yes/No) will be identified using the Covid-19 Symptoms Form of the eCRF (variables COUGH, FEVER [considered a symptom if greater than 38°], FEVERISH, STHROAT, …, ANOS) at DAY 1 to DAY 14.

- Composite of COVID-19-related hospitalization, mechanic ventilation or death in the 14 days following randomization. These events will be identified using the Adverse Events Form of the CRF:
  - ✓ COVID-19 related hospitalization: AECOVID=YES and AESER=YES and AESHOSP=YES; date of hospitalization = ADMDAT
  - ✓ COVID-19 related mechanic ventilation: AECOVID=YES and AEVENT=YES; date of mechanic ventilation = AEVSDTA
  - ✓ COVID-19 death: AECOVID=YES and AEOUT=Fatal; date of death = AEENDAT1

5 SAFETY PARAMETERS

Safety will be assessed through adverse events (AEs) and serious adverse events (SAEs).

5.1 Adverse Events

Information regarding AEs will be collected at day 3, 7, 10 and 14 after randomization. Any AEs prior to randomization will be recorded in the medical history and kept in the patients' chart. Information collected will include the onset, end date (if applicable), severity, relationship to study drug, and the management.

A treatment-emergent AE is an AE which started on or after the date of the first dose of study medication. In case the date of first dose of study medication is unknown, the AE will be assumed to be treatment-emergent if it started on or after the study medication delivery date.

In case the day the AE started is unknown (month and year are required fields for the AE start date), the AE will be assumed to be treatment-emergent if it started on the same month and year as the date of first dose of study medication (or study medication delivery date); otherwise the partial AE start date will be compared to the date of first dose of study medication (or study medication delivery date) and the AE will be classified accordingly.

A related AE is one where, according to the investigator, there is a reasonable possibility that the event may have been caused by the study drug. They will be identified from the Adverse Events Form of the eCRF as AEs that are possibly or probably related to study drug.

5.2 Serious Adverse Events

Serious Adverse Events (SAE) are those that meet any of the following International Council for Harmonisation (ICH) criteria:

- Is fatal or immediately life-threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused death had it been more severe);
- Results in persistent or significant disability/incapacity;
- Requires or prolongs patient hospitalization;
- Is a congenital anomaly/birth defect in the offspring of the patient;
- Is a cancer;
- Is an overdose (intentional or accidental);
- Is judged to be medically important.

Medically important events may not be immediately life-threatening, result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Serious adverse events are to be reported if they are known to occur within 21 days after randomization.

6 STATISTICAL METHODOLOGY

6.1 Determination of Sample Size

Sample size is based on the proportion of subjects with any of the following COVID-19 symptoms: fever, cough, shortness of breath or anosmia at day 7 since this time point will be the primary focus. Using a two-sided 0.05 significance level, sample sizes of 91 in both groups (182 total) will achieve 80% power to detect an absolute between groups difference of 20% in the proportion of subjects with the above COVID-19 symptoms at day 7. This is assuming that the proportions of patients with the above COVID-19 symptoms at day 7 will be 50% in the placebo group and 30% in the active treatment group. Factoring in a 15% drop out rate, a total of 216 patients will be randomized in the study (108 per group).

6.2 Statistical Considerations

Baseline, efficacy and safety data will be reported using descriptive statistics. N, mean, standard deviation, median, Q1, Q3, minimum and maximum will be provided for continuous variables. Count and frequency will be provided for categorical variables.

Basic assumptions of the proposed analyses will be verified prior to the analyses. Subject disposition, datasets analyzed, baseline characteristics and efficacy analyses will be carried out on the ITT population defined in Section 3.1 according to the intent to treat principle. Safety analyses will be done on the safety population defined in Section 3.2.

All statistical tests will be two-sided and conducted at the 0.05 significance level. Statistical analyses will be done using SAS version 9.4 or higher.

A fully independent 3-member Data and Safety Monitoring Board (DSMB) will be established and will review unblinded data as detailed in the DSMB charter after randomization of 50, 100 and possibly 150 subjects. The DSMB charter will pre-specify the rules for early study termination, approved by all board members.

6.2.1 Handling of Missing Data

Subjects will be asked to assess daily the presence (Yes/No) of 13 COVID-19 symptoms for a duration of 14 days. Most efficacy endpoints rely heavily on the assessment of these symptoms so a rule has to be defined in case the symptoms are reported as 'Not Done' or are missing.

At any given day (DAY 1 to DAY 14), if some symptoms among the 13 symptoms are reported as 'Not Done' or are missing, these symptoms will be imputed as the last observation carried forward.

On the other hand, if, at any given day, all symptoms are reported as 'Not Done' or are missing, the following will be done:

- If the subject has died, then all symptoms will be imputed as 'Yes' (and symptom "Fever" as greater than 38^{o}) if that day is prior to date of death.

- Otherwise, the symptoms will not be imputed and the assessment on that day will be considered missing.

6.3 Study Subjects

6.3.1 Subject Disposition

Number of subjects randomized, number of subjects who took at least one dose of study medication, number of randomized subjects completing the study and reasons for discontinuation will be summarized overall and by treatment group. A listing of subject disposition will be provided and will include subject ID, date of informed consent, date of randomization, randomized treatment group, result of the pregnancy test, day of first dose, day of last dose, completion (Yes/No), date of discontinuation and reason for discontinuation. Subject disposition will also be presented with a flow chart.

The number of days between the positive diagnosis for COVID-19 infection and the date of randomization will be summarized overall and by treatment group for the ITT population. The same will be done for the number of days between the first COVID-19 symptoms prior to randomization and the date of randomization. The first COVID-19 symptoms prior to randomization will also be displayed.

6.3.2 Protocol Deviations

Protocol deviations, as collected on the Protocol Deviation Form of the eCRF, will be summarized overall and by treatment group for the ITT population. Major protocol deviation will be summarized similarly. A listing will also be provided.

6.3.3 Datasets Analyzed

The number of subjects in each datasets will be summarized overall and by treatment group. A listing, including reason for being excluded from a given dataset, will be provided as well.

6.3.4 Demographic and Baseline Characteristics

Demographic data (age at informed consent, sex, ethnicity, race) and baseline characteristics such as physical appearance (height weight, waist circumference), medical and surgical history (smoking, diabetes, hypertension, dyslipidemia, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, stroke, heart failure, respiratory disease) as well as other past or present clinically significant medical or surgical conditions will be summarized using descriptive statistics, overall and by treatment group for the ITT population.

A listing will be presented for demographic data.

6.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded with respect to indication and generic name using the WHO Drug dictionary (version C March 2018).

Frequency of use of medications at randomization will be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment group.

A medication will be flagged as being ongoing at the time of randomization if:

- Medication start date < randomization date
  AND
- Medication end date ≥ randomization date OR Medication is ongoing

In case of missing or incomplete medication start / end dates, the following rules will be applied:

- If 1) the medication start date is completely missing or 2) only the year is specified and it is the same as the randomization year or 3) only the month/year are specified and they are the same as the randomization month/year, then the medication will be assumed to have started before randomization.
- If 1) the medication end date is completely missing or 2) only the year is specified and it is the same as the randomization year or 3) only the month/year are specified and they are the same as the randomization month/year, then the medication will be assumed to have ended after randomization.
- Otherwise, partial medication start / end dates will be compared to the randomization date and the medication will be classified accordingly.

Frequency of use of prior and concomitant medications will also be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment group.

6.3.6 Study Medication Administration

Number and proportion of subjects who received study medication, who took study medication and for whom the blinded was maintained will be provided, overall and by treatment group, for the ITT population. Number and proportion of subjects for whom study medication was prematurely discontinued, along with reason, will be displayed as well, overall and by treatment group.

Information on study medication administration will be listed.

6.4 Efficacy Analysis

All efficacy analyses will be conducted on the ITT population.

6.4.1 Primary Analysis

Number and proportion of patients with fever, cough, shortness of breath or anosmia will be summarized at 3, 7, 10 and 14 days, overall and by treatment group.

The primary analysis will compare the proportions of subjects with these symptoms between the two treatment groups using a generalized linear mixed model (GLMM), more precisely a repeated binary logistic regression model, with terms for treatment group (placebo, hesperidin), time (3, 7, 10 and 14 days) and treatment group x time interaction. Contrasts under this model will allow for the comparisons of the proportions at each time point. The primary analysis will be the comparison between treatment

groups at day 7, although treatment groups will also be compared at the other time points. Odds ratios will be provided at each time point with 95% confidence intervals and p-values.

Data for the primary endpoint will be listed.

6.4.2 Secondary Analysis

- Number of COVID-19 symptoms (range 0 – 13) will be summarized using descriptive statistics at 3, 7, 10 and 14 days, overall and by treatment group.

  Mean number of COVID-19 symptoms will be compared between treatment groups using a repeated measures analysis of variance (ANOVA) model with terms for treatment group (placebo, hesperidin), time (3, 7, 10 and 14 days) and treatment group x time interaction. Contrasts under this model will allow for the comparisons of the mean number of symptoms at each time point. Mean differences will be presented with 95% confidence intervals and p-values. If more appropriate given the distribution of the data, a Poisson regression model for repeated measures could be used.

- Number and proportion of subjects with complete disappearance of COVID-19 symptoms after randomization will be provided overall and by treatment group. In those subjects, duration of symptoms will be summarized using descriptive statistics.

  Duration of COVID-19 symptoms will be compared between treatment groups using a log rank test and Kaplan-Meier curves will be presented.

- Individual COVID-19 symptoms over time (3, 7, 10 and 14 days) will be presented and analyzed as the primary endpoint, using the statistical approach described in section 6.4.1.

6.4.3 Exploratory Analysis

- The number and proportion of subjects with each individual COVID-19 symptom will be summarized on a daily basis, i.e. at 1, 2, 3, …, 14 days, overall and by treatment group.

- In each treatment group, the incidence of the composite of COVID-19-related hospitalization, mechanic ventilation or death in the 14 days following randomization will be calculated as the number of subjects who either died, were hospitalized or required mechanic ventilation in the 14 days following randomization, divided by the number of subjects randomized to that treatment group. Number and proportion of subjects with this composite endpoint will be presented, overall and by treatment group. The incidence will be compared between treatment groups using a chi-square test. If the number of events is low, Fisher's exact test could be used.

  Since this endpoint is defined in the 14 days following randomization, the delay between an event and randomization will be calculated as date of the event (date of death, date of hospitalization or date of mechanic ventilation) – date of randomization (in days), and any event for which the delay is > 14 days will be excluded from the analysis. In case the date of the event is incomplete (the exact day could be unknown, but the month and year should be known as

they are required fields), the missing event will be assumed to occur the first day of the month, unless the randomization date is after, in which case the event will be assumed to occur the day of the randomization.

6.5 Safety Analysis

The safety analyses described in this section will be conducted on the safety population (patients who took at least one dose of study medication). Safety of hesperidin will be evaluated by presenting descriptive statistics on adverse events and serious adverse events broken down by group. No formal statistical testing is planned for the safety parameters.

6.5.1 Treatment Exposure

Duration of exposure will be defined as number of days on treatment (computed as date of last dose – date of first study drug dispensed + 1) for each subject of the safety population. Duration of exposure will be summarized overall and by treatment group. Duration of exposure will also be categorized according to 3 days intervals ([1-3], [4-6], [7-9], etc.) and summarized accordingly using frequencies and percentages, overall and by treatment group.

6.5.2 Adverse Events and Serious Adverse Events

6.5.2.1 Adverse Events

AEs will be coded by system organ class and body system according to the MedDRA dictionary (version 23.1).

The total number of TEAEs reported, the number and proportion of subjects experiencing at least one TEAE, at least one severe TEAE, at least one TEAE related to the study treatment, and at least one TEAE leading to drug withdrawal will be presented. In addition, number and proportion of subjects experiencing a treatment-emergent AE will be presented by system organ class, preferred term and severity overall and for each treatment group.

All AEs will be listed but only treatment-emergent AEs will be summarized. Listing will include Subject ID, age, gender, date of beginning of treatment, name and preferred term of AE, start and stop date, severity, relationship to study drug and outcome.

6.5.2.2 Serious Adverse Events

Serious adverse events will be presented similarly to AEs as described in section 6.5.2.1.

A separate listing for deaths will be provided. This listing will include subject ID, age, gender, date of beginning of treatment, date of death, phase of the study during which death occurred as well as the cause of death.

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8 APPENDICES

APPENDIX A COVID-19_ SYMPTOMS LOG

Symptoms	Day 1 Yes No	Day 2 Yes No	Day 3 Yes No	Day 4 Yes No	Day 5 Yes No	Day 6 Yes No	Day 7 Yes No
Recent cough or aggravation of chronic cough	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Fever (enter temperature)							
Feverish/chills (temperature not taken)	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Sore throat	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Runny nose	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Shortness of breath/difficulty breathing	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Nausea/vomiting	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Headache	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
General weakness	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Pain (muscular, chest, abdominal, joint, etc.)	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Irritability/confusion	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Diarrhea	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Sudden Loss of smell (anosmia)	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Comment or other, specify:							

Reminder: Please have the completed diary on hand at each phone call or video contact follow up.

Symptoms	Day 8 Yes No	Day 9 Yes No	Day 10 Yes No	Day 11 Yes No	Day 12 Yes No	Day 13 Yes No	Day 14 Yes No
Recent cough or aggravation of chronic cough	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Fever (enter temperature)							
Feverish/chills (temperature not taken)	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Sore throat	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Runny nose	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Shortness of breath/difficulty breathing	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Nausea/vomiting	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Headache	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
General weakness	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Pain (muscular, chest, abdominal, joint, etc.)	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Irritability/confusion	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Diarrhea	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Sudden Loss of smell (anosmia)	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐	☐ ☐
Comment or other, specify:							

Reminder: Please have the completed diary on hand at each phone call or video contact follow up.

APPENDIX B TIMETABLE OF VISITS AND PROCEDURES

Visits	1. Screening / randomization (Phone call)	2. Contact Point (Phone) – no window	3. Contact Point (Phone) (± 1 day)	4. Contact Point (Phone) (± 3 days)	5. Contact Point (Phone call) (± 3 days)
Days	0	3	7	10	14
Informed consent	X				
Demographics	X				
Medical/Surgical history	X				
Review concomitant medication	X	X	X	X	X
Covid-19 symptoms (including date of onset)	X	X	X	X	X
Review Inclusion/Exclusion criteria	X				
Urinary pregnancy test*	X				
Randomization	X				
Record potential study endpoints and other AEs		X	X	X	X
Study medication dispensing	X				
Study medication compliance		X	X	X	X

*For women of childbearing potential
**If day 3 occurs on the weekend, contact point will be done on previous Friday or following Monday, whichever is closer to day 3.