Master Protocol for Early Treatment and Post-Exposure Prophylaxis of COVID-19 Adaptive Platform Trial

PROTECT-APT 1

Protocol Number: PC06

Sponsored by: FHI Clinical

Funded by: Joint Program Executive Office (JPEO)

Implemented by: The Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. (HJF)

Industry Supporters:

Study Chair: Danielle Clark

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Version 5.0

07 Feb 2024

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Version and Date	Affected Section(s)	Summary of Revisions Made	Rationale
V 5.0 07 Feb 2024	3.2 Background	Added rationale for expansion of the study population to standard and intermediate risk	Rational to support study population expansion
V 5.0 07 Feb 2024	5.2 Shared Groups	Clarified the ability for PSAs to choose to participate or not participate in placebo sharing Clarified participants must meet final eligibility criteria for all PSAs for which they are eligible and contributing to a shared placebo pool	Clarification on placebo sharing for PSAs and participants
V 5.0 07 Feb 2024	7.4.1 Randomization	Clarified the ability for PSAs to choose to participate or not participate in placebo sharing Clarified participants must meet final eligibility criteria for all PSAs for which they are eligible and contributing to a shared placebo pool	Clarification on placebo sharing
V 5.0 07 Feb 2024	7.4. Randomization, Figure 3	Updated figure to clarify flow for participant eligibility for multiple PSAs contributing to shared placebo pool	Clarification on placebo sharing
V 5.0 07 Feb 2024	14.1.2 Informed Consent Process and Informational Documents Provided to Participants	Clarified that participants must complete PSA informed consent for all PSAs for which they may be eligible and are contributing to a shared placebo pool	Clarification on participant eligibility assessment for placebo sharing
V 5.0 07 Feb 2024	9.4.2 Enrollment Visit – In Person (Day 0)	Clarified order of activities to reflect Informed Consent and MP/PSA screening assessments	Clarification on order to activities for participants to complete PSA ICF and eligibility assessments prior to Step 1 randomization

Version and Date	Affected Section(s)	Summary of Revisions Made	Rationale
V 5.0 07 Feb 2024	6.2 Exclusion Criteria Population A	Expanded study population to include standard and intermediate risk participants (revised high risk exclusion criteria per FDA Type D Meeting Request Written Response)	FDA feedback to Type D Meeting Request
V 5.0 07 Feb 2024	9.2.3 Screening Assessments	Clarified screening assessments under the Master Protocol	Clarification of requirements for screening under Master Protocol

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

USG funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of USG-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator Name:			
Site Investigator Title:			
Signature:		**Date:**	

1 PROTOCOL SUMMARY

1.1 Study Synopsis

Early Treatment and Post-Exposure Prophylaxis of COVID-19 - Adaptive Platform Trial

Design	This study is an adaptive, randomized, double blind, platform trial evaluating promising investigational products (IP) for safety and efficacy as early outpatient treatment and post-exposure prophylaxis for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This multicenter trial will be conducted in both domestic and international sites. The study will compare IPs to control in standard and intermediate risk, non-hospitalized adult SARS-CoV-2 infected participants and uninfected adult contacts of SARS-CoV-2 confirmed cases. The master protocol will outline the core elements of the study. Investigational products may be included in either or both study indications: early treatment and post-exposure prophylaxis (PEP). The study includes a phase 2 evaluation for all IPs. The platform trial design will allow for multiple IPs to be incorporated into the protocol as product specific appendices (PSA) as products are identified and become available. Each PSA will detail the interventions, the endpoints, target treatment effect, intended statistical analysis, the relevant control arms, and the sample size range. The PSA may define additional adaptive design elements, such as early declaration rules.
Regimen	IPs for early treatment and/or post-exposure prophylaxis will be selected by the study investigators for inclusion based on the review of in vitro data demonstrating anti-SARS-CoV-2 therapeutic efficacy in pre-clinical and early clinical testing, and adequate safety data for the indication. Products included in the study for an alternate indication (such as post-exposure prophylaxis) will also be chosen based on similar evaluations of efficacy, and safety of the initial indication. Selection will also be based on product availability. Dosing regimens will be outlined in PSAs and Informed Consent Forms (ICFs).
Duration	In person and remote follow up will occur twice a week through Day 14 then at Day 28 and Week 12. Variations to the master protocol schedule will be outlined in product specific appendices and ICFs.
Stratification	Participants will be stratified as SARS-CoV-2 positive (cases) or SARS-CoV-2 negative (contacts) after completion of a screening process. SARS-CoV-2 positive cases will be placed in the Early Treatment indication and the SARS-CoV-2 negative close contacts of symptomatic SARS-CoV-2 positive cases will be placed in the PEP indication.

Randomization	Two step randomization. After completion of the screening process, participants will be stratified into the appropriate indication of the trial (Early Treatment for SARS-CoV-2 positive cases and PEP for close contacts of SARS-CoV-2 positive cases). The first randomization will be to an appropriate PSA for which participants are eligible (meeting product-specific inclusion and exclusion criteria). Participants must be eligible for at least one PSA enrolling in that indication. The first randomization will not be blinded. The second randomization will be to the arms within the PSA (IP or control). The second randomization will be blinded.
Study Population	Population A: Symptomatic, standard and intermediate risk, non-hospitalized SARS-CoV-2 infected adults (≥18 years) Population B: SARS-CoV-2 uninfected adult contacts
Sample Size	The sample size for each product will be detailed in each PSA.
Outcome Measures	The primary efficacy assessment in the early treatment indication will be time to sustained alleviation or resolution of COVID-19 symptoms The primary efficacy assessment in the post-exposure prophylaxis indication will be incidence of COVID-19 infection

1.2 Schedule of Activities (SoA)

STUDY VISIT LOCATION [A]	IN PERSON OR REMOTE [b]	IN PERSON	IN PERSON OR REMOTE		REMOTE	IN PERSON		IN PERSON OR REMOTE	
STUDY PROCEDURES	SCREENING [c]	ENROLLMENT D0	D3 [d]	D7 [d]	D10	D14	D28	WEEK 12	UNSCHEDULED [e]
VISIT WINDOW (+/- DAYS OR WEEKS)	**UP TO 24 HOURS PRIOR TO ENROLLMENT**	0	1 DAY	1 DAY	1 DAY	2 DAYS	4 DAYS	2 WEEKS	**NOT APPLICABLE**
SCREENING & PROCEDURES									
Screening Informed Consent	X								
Demographics [f]	X	X							
Medical History [f]	X	X							
Vital Signs [f]	X	X							
Physician Exam [f, g]	X	X							
Height and Weight [f]	X	X							
SARS-CoV-2 Vaccination History [f,i]	X	X	X	X		X	X	X	X
Screening Symptom Questionnaire [f fh,i]	X	X							
Concomitant Medication Review [f,i]	X	X	X	X	X	X	X	X	X
Venous Blood Sampling	X	X							
Screening Laboratories [j,o]	X	X							
Upper respiratory Specimen [f,]	X	X							

STUDY VISIT LOCATION [A]	IN PERSON OR REMOTE [b]	IN PERSON	IN PERSON OR REMOTE		REMOTE	IN PERSON		IN PERSON OR REMOTE	
STUDY PROCEDURES	SCREENING [c]	ENROLLMENT D0	D3 [d]	D7 [d]	D10	D14	D28	WEEK 12	UNSCHEDULED [e]
VISIT WINDOW (+/- DAYS OR WEEKS)	**UP TO 24 HOURS PRIOR TO ENROLLMENT**	0	1 DAY	1 DAY	1 DAY	2 DAYS	4 DAYS	2 WEEKS	**NOT APPLICABLE**
Diagnostic Test for SARS-CoV-2 [f,l,k]	X	X							
Pregnancy Test [f,m,i]	X	X	When pregnancy is suspected						
PSA (IP) Informed Consent [n]		X							
PSA Screening and Eligibility [o]		X							
Randomization (Step 1)		X							
Randomization (Step 2)		X							
Dispense Study Kit [p]		X							
Collect and Update Contacts		X	X	X					
TREATMENT or PROPHYLAXIS									
Administer IP or Control		X	Refer to PSA						
EFFICACY									
Daily Follow Up Symptom Questionnaire [q]			Daily					X	X
Upper Respiratory Specimen [r]		X [u]	X	X	X	X	X	X	X
Clinical Outcome Assessment			X	X	X	X	X	X	X

Study Visit Location [A]	In Person or Remote [b]	In Person	In Person Or Remote		Remote	In Person		In Person or Remote	
Study Procedures	Screening [c]	Enrollment D0	D3 [d]	D7 [d]	D10	D14	D28	Week 12	Unscheduled [e]
Visit Window (+/- days or weeks)	**Up to 24 hours prior to Enrollment**	0	1 day	1 day	1 day	2 days	4 days	2 weeks	**Not Applicable**
SAFETY									
Vital Signs		X	X	X		X	X	X	X
Physical Exam [g]		X	X	X		X	X	X	X
Venous Blood Sampling									
Hematology		X [u]	X	X		X	X	X	X
Blood Chemistry		X [u]	X	X		X	X	X	X
Adverse Events		X	Continuous						X
RESEARCH LABS and PHARMACOKINETICS									
Storage for Future Research [s,t]			Refer to PSA						
Pharmacokinetics			Refer to PSA						

a. In person visits may include those that take place at the research site, home visits or visits to participants admitted to hospital for social, quarantine or isolation purposes. Remote visits may take place over the phone or by video conferencing.
b. If remote visit not feasible or is not permitted under local regulation, the visit may be conducted in person.
c. If screening visit conducted remotely, screening activities not completed at the Screening visit will be completed at Enrollment. Screening and Enrollment activities may take place on the same day.
d. Day 3 and Day 7 Visits may be Remote or In Person. In person visits may include those that take place at the research site, home visits or visits to participants admitted to hospital for social, quarantine or isolation purposes. Remote visits may take place over the phone or by video conferencing. Activities completed during these visits will be dependent on visit type (remote or in person). Refer to PSAs for the location of the visit and the procedures to be conducted during the visit.
e. For Unscheduled Visits - These procedures may be done according to clinical judgement.
f. These activities may take place at screening or enrollment. Activities completed at screening do not need to be repeated at enrollment
g. Physical exam will be performed by a healthcare professional qualified in the clinical practice of medicine. This may include physicians, nurses, or other allied health professionals who are registered/licensed in the local jurisdiction and the performance of a physical exam is within the current scope of practice. Physical exam may be conducted in person or via a research staff-assisted telehealth physical exam as specified in the PSAs.
h. The Screening Symptom Questionnaire may be completed at Screening if performed on same day as Enrollment. If Enrollment does not take place on the same day as Screening, then Screening Symptom Questionnaire will be repeated at Enrollment. Results of the questionnaire will be used to determine final eligibility for enrollment.
i. Final eligibility will be determined upon completion of these activities. For activities completed at Screening, results will be reviewed and verified at enrollment to determine eligibility.
j. Screening laboratory requirements (if any) will be detailed in the PSA.
k. Omit at screening if documentation of SARS-CoV-2 test results are available.
l. Diagnostic testing must be an approved molecular or antigen diagnostic test for SARS-CoV-2 from any upper respiratory specimen performed at screening or enrollment or within 5 days of enrollment. The test used must be authorized for use by the relevant national authority for the detection of SARS-CoV-2 in the country where the test is administered. Test kits can be obtained from a locally acquired source. Historical testing results will be acceptable if testing performed within the required window. The local testing result, specimen type, assay type, and date of test will be recorded in the CRF. The test result must be available and reviewed by site PI or study staff to confirm eligibility.
m. Pregnancy testing will be completed in all females of childbearing potential defined as premenopausal females capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception and women whose male sexual partners have been vasectomized or are using contraceptive devices. If screening and enrollment are not conducted on the same day, then pregnancy testing will not be repeated for enrollment. Pregnancy testing may be performed with serum or urine and must be authorized for use by the relevant national authority for the detection of pregnancy in the country where the test is administered.
n. Participants will complete informed consent for all PSAs enrolling in their strata for which they may be eligible.
o. Participants will complete all PSA specific screening assessments for which they have consented to determine final eligibility. PSAs for which the participant meets the eligibility criteria will be included in the Step one randomization
p. Study Kit will include the following:
    - Copy of informed consent
    - Study information

- Contact information for study staff and IND Sponsor
- Daily Follow Up Symptom Questionnaire – paper version or smart device form as preferred by participant (See Supplement 2)
- Supplies and instructions for specimen self-collection

q. The Daily Follow Up Symptom Questionnaire will be completed by the participants on designated days (Supplement 2). The Daily Follow Up Symptom Questionnaire may be delivered and completed electronically via push reminder to participants at the same time each day. Paper forms may also be dispensed to study participants unable to complete the form electronically. Study staff will input the data from the paper forms into the CRF and may also contact the participant and remind them to complete the survey.

r. For in person visits upper respiratory specimens may be collected by research staff or self-collected by participant with research staff assistance (if needed). For remote visits specimens will be self-collected by participants.

s. Not all blood collected will be used for testing in this study but will be stored to be used in testing for future studies. Section 9.2.4 Stored Specimens outlines the potential future testing for each blood type collected.

t. With participant consent.

u. Prior to administration of IP or control

2 STUDY MANAGEMENT

FHI Clinical (FHIC) will serve as the study sponsor (hereinafter referred to as the Investigational New Drug (IND) sponsor). FHIC will be responsible for activities related to the regulatory approval, study implementation, study execution, data collection and study monitoring.

The Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. (HJF) will serve as the study implementer. HJF will be responsible for protocol design and development, medical writing, study oversight and serve as a study specimen repository.

3 INTRODUCTION

3.1 Study Rationale

SARS-CoV-2, a member of the beta coronavirus family, was first identified in China in December 2019 and is responsible for coronavirus disease 2019 (COVID-19) [Zhu 2019]. The World Health Organization declared the novel coronavirus outbreak a pandemic in March of 2020 [Cucinotta 2020]. The high transmissibility, varying degrees of symptom manifestation, high case fatality rate, and emergence of viral variants make disease control and prevention challenging.

Early outpatient treatment and post exposure prophylaxis can reduce disease severity and prevent disease transmission. While several classes of therapeutics and vaccines are currently available as treatment and prophylaxis against COVID-19, the rise of viral variants has led to reduced efficacy of these measures and immune escape by the virus [Yamasoba 2022, Cao 2022, Willett 2022]. Further, many of the approved therapies target hospitalized cases. A limited number of options are available for early outpatient treatment and post-exposure prophylaxis of COVID-19. Continuing research is needed to address this gap in the face of ongoing surges of COVID-19 infections and continuing emergence of viral variants.

3.2 Background

In December 2019, a cluster of atypical pneumonia attributed to a novel coronavirus, SARS-CoV-2, was reported in the city of Wuhan in the Hubei Provence of China [Zhu 2019]. As of Jan 1st, 2023, there have been over 600 million cases and 6 million deaths globally due to COVID 19 [Johns Hopkins University 2023]. Symptoms associated with SARS-CoV-2 infection are varied and can range from asymptomatic infection to acute respiratory failure [Mudatsir 2020]. The most commonly reported symptoms of COVID-19 infection include cough, fever, and fatigue [Akaishi 2022, Zhang 2022]. The incubation period ranges from 2 to 17 days with a mean of 6 days, although shorter incubation periods have been reported with recent variants of concern (VOC) [Elias 2021, Jansen 2021]. Risk factors for progression to severe disease and death from COVID-19 include age and presence of comorbidities such as chronic lung disease, diabetes, chronic kidney disease and obesity [CDC 2022].

Significant focus has been placed on efforts to limit the spread of SARS-CoV-2. Attack rates range from 0.8% with asymptomatic index cases to 18% in symptomatic index cases [Toth 2021]. Recent Variants of Concern (VOC) have secondary attack rates as high as 30%, even among fully vaccinated individuals [Lim 2022, López-Muñoz 2022]. One major challenge in limiting disease transmission is infected individuals are more likely to transmit the virus in the early or pre-symptomatic stages of illness. It is estimated that SARS-CoV-2 infectiousness peaks two days before to one day after onset of symptoms and declines within 6 days of symptom onset [Cheng 2020].

Several nonpharmaceutical interventions have demonstrated effectiveness for limiting SARS-CoV-2 infection and various levels of these interventions have been adopted by countries throughout the globe. These include travel restrictions, quarantine of travelers arriving from

affected countries, restrictions of mass gathering, isolation and quarantine of confirmed cases and close contacts, social distancing measures, compulsory mask wearing, contact tracing and testing, school closures and use of personal protective equipment among health workers [Ayouni 2021]. These measures, however, have high social, healthcare, and economic costs [Askitas 2021].

Introduction of vaccines against SARS-CoV-2 have had a significant impact on disease incidence and disease spread [Britton 2021, Lopez 2021]. While vaccination remains an effective way to prevent SARS-CoV-2 infection, many countries, populations, and individuals do not have access to or decline vaccination [Brown 2021]. In addition, multiple studies have demonstrated waning immunity to SARS-CoV-2 several months following vaccination, among certain populations at high risk for development of severe disease, and against viral variants [Willett 2022, Hewins 2022, Martinuzzi 2022].

With the evolution of the pandemic has come the emergence of SARS-CoV-2 variants that have exhibited increased transmissibility and virulence [SARS-CoV-2 Variant Classifications and Definitions]. Several monoclonal antibodies and antivirals have been approved for the early treatment and prophylaxis of SARS-CoV-2 infection. However, continued mutation of the virus has led to increasing resistance to immune responses and varying efficacy of these therapies [Yamasoba 2022, Cao 2022, Weisblum 2020, Starr 2021, Chen 2021]. This has resulted in removal of therapies for approved use or placing of limitations on their indication [Cavazzoni 2022]. Current treatment guidelines recommend symptomatic care for low or standard risk patients who do not require hospitalization or supplemental oxygen. The guidelines also recommend against the use of dexamethasone or other systemic steroids in this population. For those who are at high risk to progress to severe disease the guidelines recommend therapies including antivirals (Ritonavir-boosted nirmatrelvir (Paxlovid), remdesivir, and molnupiravir) [COVID-19 Treatment Guidelines 2022]. However, increase use, coupled with continued mutation of the virus, has led to concerns of development of resistance to these therapies [Service 2022, Sedova 2022, Jochmans 2022].

There remains an unmet medical need in prevention and treatment of outpatients with COVID-19. Significant research has been directed at the prevention of hospitalization and death in patients at high risk for progression to severe disease. However, 50-60% of infections occur in standard risk outpatients with SARS-CoV-2 infection [Koma 2023]. Currently, there are no approved therapies for these patients at standard risk for progression to severe disease [COVID-19 Treatment Guidelines 2022]. In 2022 alone, 316 million working days were lost due to the COVID pandemic, the majority (191 million) were due to acute mild or moderate illness [Berdan 2023]. Similarly, for intermediate risk patients, in many regions globally, currently approved therapies are not accessible or available. In addition, numerous drug-drug interactions and contraindications, limit the use of these medications in infected patients. The ongoing evolution of SARS-CoV-2 and the continued emergence of resistance to vaccines and therapies by viral variants has highlighted the need for ongoing research and new therapies to treat COVID-19 and prevent its continued spread. Additionally, there is a gap in available outpatient treatment options that shorten disease duration for standard and intermediate risk patients. This study will investigate the safety and efficacy of promising investigational products for both early outpatient treatment and post-exposure prophylaxis for SARS-CoV-2. The study will focus on

inclusion of products with broad neutralizing and antiviral activity, ease of administration, and potential to avoid SARS-CoV-2 variant escape.

3.3 Study Hypothesis

Early Treatment: The primary hypothesis is that early treatment with IP among standard and intermediate risk outpatients infected with SARS-CoV-2 can shorten time to sustained symptom alleviation or resolution compared to standard care.

Post-exposure Prophylaxis: The primary hypothesis is that post-exposure prophylaxis with IP can prevent COVID-19 infection among close contacts of symptomatic SARS-CoV-2 positive cases compared to standard care.

3.4 Risk/Benefit Assessment

3.4.1 Known Potential Risks

The risks of study participation may include:

- Phlebotomy can infrequently cause temporary bruising, erythema, pain, infection, or bleeding.
- Upper respiratory specimen collection – upper respiratory swabs may cause the participant to gag, cough, or vomit. The swab may cause some discomfort or mild bleeding.
- Loss of confidentiality.
- Product specific risks are defined in the product specific appendices.

Steps taken to minimize risks:

- To diminish the risks of phlebotomy, only adequately trained study personnel will draw venous blood.
- Blood volumes taken from the study participants will fall within the Human Research Protection Office (HRPO) guidelines.
- Only adequately trained study personnel will collect upper respiratory specimens, collection may be self-administered after appropriate instruction.
- See Section 14.1.5 Confidentiality and Privacy.

3.4.2 Known Potential Benefits

Direct Benefits:

Study participants are not guaranteed benefit. Investigational products may decrease the severity of COVID-19 disease in exposed or infected individuals and may prevent infection with SARS-CoV-2 altogether. Information gained from this study will inform product development decisions.

Participants in the study will be enrolled early in illness onset or soon after a SARS-CoV-2 case is identified, and they will be closely monitored. Early medical evaluation and regular monitoring of COVID-19 could offset the severe consequences of the disease. Diagnostic test results may be provided to study participants faster than results obtained through routine clinical care.

Indirect Benefits:

Participation in the study will help provide information about the benefits of early treatment and post-exposure prophylaxis therapy for COVID-19.

3.4.3 Assessment of Potential Risks and Benefits

Known potential risks and benefits of each IP (also referred to as study drug or intervention) will be described in the product specific appendices. They will include the rationale for the necessity of exposing participants to risks, summary of the plan to minimize risk to participants and risk benefit justification.

4 OBJECTIVES AND ENDPOINTS

This section is a summary of the of the primary endpoints for the early treatment and post-exposure prophylaxis indications. Each PSA will include a more detailed discussion of the primary endpoints in addition to presentation of secondary, safety and any exploratory endpoints.

4.1 Early Treatment

	Objective	Endpoint
Primary	To determine if early treatment with IP can shorten time to sustained symptom alleviation or resolution in participants infected with SARS-CoV-2	• Time to sustained alleviation or resolution of COVID-19 symptoms o Defined as the number of days from randomization in a PSA to the first day the participant reports all symptoms as mild or none (or returning to pre-illness levels) for at least 3 consecutive days (the first day being considered the Event Day). [Timeframe: Day 0 to Day 28]
Key Secondary	To evaluate the clinical efficacy of IP compared to control	• Number and proportion of all cause hospitalizations • Number and proportion of all cause deaths [Timeframe: Day 0 to Day 28]
Safety	To evaluate the safety and tolerability of IP compared to control	• Incidence of Serious Adverse Events (SAE) • Comparison between active and placebo treatment groups in proportion of all and ≥Grade 3 AEs as assessed by the National Institutes of Health, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (NIH, DAIDS AE Grading Table), corrected Version 2.1, July 2017. • Incidence of AEs causing IP discontinuation • Incidence of all-cause IP discontinuation or interruption • Incidence of Adverse Events of Special Interest (AESI) (if applicable to PSA) • Number of participants hospitalized due to adverse events regardless of cause

Refer to PSA for additional IP specific objectives and endpoints

4.2 Post-Exposure Prophylaxis

	Objective	Endpoint
Primary	To determine if post-exposure prophylaxis with IP can reduce incidence of symptomatic COVID 19 infection	• Proportion of participants who develop COVID-19 infection by Day 14 ○ Defined as positive RT-PCR test **and** presence of at least one COVID-19 symptom
Safety	To evaluate the safety and tolerability of IP compared to placebo	• Incidence of Serious Adverse Events (SAEs) • Comparison between active and placebo treatment groups in proportion of all and ≥grade 3 adverse events as assessed by the National Institutes of Health, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017. • Incidence of AEs causing IP discontinuation • Incidence of all-cause IP discontinuation or interruption • Incidence of Adverse Events of Special Interest (AESI) (if applicable to PSA) • Number of participants hospitalized due to adverse events regardless of cause

Refer to PSA for additional IP specific objectives and endpoints.

5 STUDY DESIGN

5.1 Overall Design

This study is an adaptive, randomized, double blind, platform trial evaluating promising investigational products (IP) for safety and efficacy as early outpatient treatment and post-exposure prophylaxis for SARS-CoV-2. This multicenter trial will be conducted in both domestic and international sites. The study will compare IPs to standard of care in non-hospitalized SARS-CoV-2 infected participants and uninfected adult contacts of SARS-CoV-2 confirmed cases. The master protocol is described here and outlines the core elements of the study. The study includes a phase 2 evaluation for all IPs. Phase 2/3 or phase 3 evaluations may be included as amendments to the MP and detailed in the PSA.

Investigational products may be evaluated for either or both study indications: early treatment and/or post-exposure prophylaxis (PEP). The platform trial design will allow for multiple IPs to be incorporated into the protocol as product specific appendices (PSA) as products are identified and become available. An independent Data and Safety Monitoring Board (DSMB) will monitor the study both for futility and early efficacy to manage participant risk appropriately.

Each PSA will detail the interventions, intended study phase, the endpoints, target treatment effect, intended statistical analysis, the relevant control arms, and the sample size range. The PSA may define additional adaptive design elements, such as early declaration rules. The DSMB will monitor interim data and the adaptive designs to make recommendations about early study closure or adaptive elements to the PSA.

Safety will be evaluated based on clinical laboratory studies, vital signs, assessment of adverse events (AEs), symptom monitoring and physical exams. Efficacy will be evaluated based on viral testing, symptom scoring and outcome ascertainment.

5.1.1 Selection of Investigational Products

Investigational products for inclusion will be selected based on review of the preclinical and early clinical data. Review will evaluate safety, tolerability, and efficacy of the IP. Two physicians will determine eligibility based on review of available data. Review will include evaluation of the following:

- In vitro assays and in vivo studies demonstrating anti-SARSCoV2 activity
- Treatment emergent adverse events (TEAE)
- Infusion related reactions (for intravenous products), hypersensitivity reactions
- Completion of optimum dose selection and tolerability studies
- PK studies of bioavailability, neutralizing-level serum concentrations appropriate for early treatment or PEP, and time to maximum serum concentration
- In vitro and/or in vivo studies demonstrating efficacy against currently circulating VOC
- Development of anti-drug antibodies/ neutralizing ab to IP

Selection will also be based on route of administration and product availability. Products with oral, subcutaneous, and intramuscular delivery modes may be prioritized due to acceptability, and feasibility of administration. If after the review, the two physicians cannot agree on a decision to include or exclude the IP in the trial, adjudication will be performed by a third physician.

5.1.2 Period of Evaluation

Participants will be followed for a period of up to 12 weeks. Safety evaluations will include monitoring of symptoms and adverse events throughout the study period. Efficacy evaluations will include prevention of SARS-CoV-2 infection and symptom duration in exposed contacts, and reduction in viral load and COVID-19 symptom severity in SARS-CoV-2 positive cases.

5.1.3 Early Termination

An external Data Safety Monitoring board (DSMB) will review adverse events and safety information and may recommend early termination based on this review. Additionally, the interim analyses detailed in the PSAs will detail early study declaration for superior efficacy, futility or if there is a safety signal.

5.2 Shared Groups

One of the primary advantages of the platform design is the ability to share control groups among different PSAs. For example, if two PSAs are enrolling PEP participants, each with a placebo control group, the analysis of each may include the placebo participants from the other PSA. To be eligible to contribute to a shared placebo pool, participants must meet the eligibility criteria for all PSA's contributing to that shared pool. PSAs may choose not to participate in placebo sharing. PSA contribution to a shared placebo pool will be determined prior to commencement of enrollment for that PSA.

Each PSA will define the intervention, primary analysis, and the relevant control group. For analysis, the control group will include all participants randomized to the placebo control arm from all PSAs contributing to the shared placebo pool and meeting the eligibility criteria for the PSA being analyzed. If participants are eligible for only a subset of PSAs enrolling in that stratum, the statistical analyses for that PSA will be based on comparisons against only those control arm participants who were eligible for that PSA.

5.3 Scientific Rationale for Study Design

The purpose of this investigation is to evaluate the safety and efficacy of promising investigational products for early outpatient treatment and post-exposure prophylaxis for SARS-CoV-2.

5.4 Justification for Dose

Refer to appendix/appendices for details of investigational products.

5.5 End of Study Definition

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in Section 1.2 Schedule of Activities (SoA).

This platform trial will be conducted until all PSAs have concluded and all participants within all PSAs have completed follow up.

6 STUDY POPULATION AND STUDY ENROLLMENT

The target populations for the study are:

A. Non-hospitalized SARS-CoV-2 infected adults

B. Uninfected adult SARS-CoV-2 contacts

6.1 Inclusion Criteria

Individuals who meet the following criteria may be included in the study:

Population A: Symptomatic adults seeking care or testing for COVID-19.

1) Age ≥ 18 years
2) Positive molecular or antigen diagnostic test for SARS-CoV-2 at study enrollment or within ≤ 5 days prior to enrollment
3) Presence of two or more Screening Symptoms listed in Supplement 3 with at least two symptoms classified as moderate to severe (and/or ≥ 2 on the frequency questions or loss of taste/smell questions) at the time of enrollment
    a) For participants who have preexisting conditions causing mild or moderate symptoms listed on the Screening Symptom Questionnaire, there must be an increase of at least one severity level for that symptom at enrollment (For example, prior to illness participant routinely experienced headaches rated as moderate severity, now rating headache as severe at enrollment)
4) Symptom onset ≤ 5 days prior to enrollment

Population B: Uninfected adult contacts of symptomatic SARS-CoV-2 infected individuals

1) Age ≥ 18 years
2) Asymptomatic contact of an individual with laboratory confirmed SARS-CoV-2 infection defined as:
    a) Indoor exposure to the symptomatic case or cases within 6 feet (2 meters) for ≥ 15 minutes over a 24-hour period without the use of personal protective equipment
3) Negative screening SARS-CoV-2 molecular or antigen diagnostic test performed at screening or within less than or equal to 24 hours of enrollment
4) Exposure and enrollment within 6 days or less from when the symptomatic, confirmed SARS-CoV-2 positive case first had symptoms

For Both Populations

1) Must also meet the intervention specific inclusion/exclusion criteria for at least one PSA that is enrolling participants.

6.2 Exclusion Criteria

This study will exclude individuals who meet any of the following criteria:

Population A: Symptomatic adults seeking care or testing for COVID-19

1) Hospital admission at the time of enrollment
2) Hospitalization will be defined as requiring medical care not available in an outpatient setting for greater than 24 hours.
3) Hospitalization for isolation or quarantine requirements or for social reasons will NOT constitute an exclusion criterion
4) Laboratory confirmed SARS-CoV-2 infection 6 to 90 days prior to enrollment
5) Oxygen saturation < 92% on room air
6) Baseline use of supplemental oxygen at the time of enrollment
7) Presence of any of the following comorbidities that per the PI puts the patient at high risk of developing severe COVID-19 illness:
    a) Age ≥ 75 years
    b) Active treatment for solid tumor and hematologic malignancies
    c) Hematologic malignancy, myeloma, or related disorder (e.g., myelodysplastic syndrome, myelofibrosis)
    d) Receipt of solid-organ transplant or an islet transplant and taking immunosuppressive therapy
    e) Chemotherapy or radiotherapy for solid organ cancer in last 12 months
    f) Receipt of chimeric antigen receptor (CAR)-T-cell therapy or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppressive therapy)
    g) Moderate or severe primary immunodeficiency (e.g., common variable immunodeficiency disease, severe combined immunodeficiency, DiGeorge syndrome, Wiskott-Aldrich syndrome)
    h) Advanced or untreated HIV infection (people with HIV and CD4 cell counts less than 200/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
    i) Active treatment with high-dose corticosteroids (i.e., 20 or more mg of prednisone or equivalent per day when administered for 2 or more weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor necrosis factor (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory
    j) Sickle cell disease
    k) Chronic liver disease (e.g., Child-Pugh Class A, B or C cirrhosis)
    l) Down syndrome

m) Dementia or neurocognitive disability (e.g., Parkinson's disease)

n) Participants with 3 or more of the following conditions:

i) No prior COVID-19 infection OR has not completed a COVID-19 vaccine series within the last 6 months OR has not received a vaccine booster within the last 6 months

ii) Age 65-74 years

iii) BMI ≥35 (or >95th percentile in adolescents)

iv) Type 1 or type 2 diabetes mellitus

v) Cardiovascular disease (including HTN if age >55)

vi) Chronic lung disease (including bronchiectasis, CF, COPD, ILD, PHTN, PE, moderate-to-severe asthma)

vii) Chronic kidney disease (eGFR <30)

8) Participants who are receiving or plan to receive anti-SARS-CoV-2 antivirals for treatment of their COVID-19

Population B: Post-exposure adult contacts of SARS-CoV-2 infected Individuals

1) Symptoms attributed to COVID-19 as assessed by the investigator
2) Positive molecular or antigen diagnostic test for SARS-CoV-2 from any upper respiratory specimen within 90 days prior to enrollment
3) SARS-CoV-2 vaccination within 90 days prior to enrollment EXCEPT if severely immunocompromised or a known vaccine non-responder
4) Severely immunocompromised or a known vaccine non-responder defined as: solid organ or stem cell transplant recipient, B cell leukemia, receiving B cell depletion therapy (e.g., rituximab), agammaglobulinemia, or negative serology ≥2 weeks after vaccination with two doses of a vaccine
5) Hospital admission at the time of enrollment
   a) Hospitalization will be defined as requiring medical care not available in an outpatient setting for greater than 24 hours.
6) Hospitalization for isolation or quarantine requirements or for social reasons will NOT constitute an exclusion criterion

For Both populations:

1) Absence of informed consent
2) Pregnancy
3) Breastfeeding
4) Individuals who the study investigators believe are unable to comply with the requirements of the study

5) Participation in another intervention trial for the treatment or prophylaxis of SARS-CoV-2 infection or COVID-19 disease at the time of enrollment

Any product-specific exclusion criteria will be added in the product specific appendices.

6.3 Lifestyle Considerations

During this study, participants are asked:

1) Not to participate in another clinical trial with an IP for the duration of their enrollment in the trial

Refer to appendix/appendices for investigational product specific considerations

Refer to appendix/appendices for investigational product specific co-enrollment guidelines

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in this study but do not meet entry criteria for the study. Individuals who do not meet the criteria for participation in this study (screen failure) because of not meeting one or more of the entry criteria that are likely to change over time may be rescreened. Rescreened participants will be assigned a new participant number.

6.5 Strategies for Recruitment and Retention

Study participants will be recruited from collaborating healthcare systems and shared or congregate living arrangements. Recruitment may be conducted at healthcare facilities, community health clinics, or drive through testing centers affiliated with the healthcare system, and/or health system registries.

The study team will use multiple means of communicating study awareness to enhance recruitment efforts, including periodic briefings delivered by the site Principal Investigator (PI)s or their study teams to the clinical trial site staff. If permitted, information notices with points of contacts will be posted or distributed at recruitment locations.

Clinical trial sites may also use existing SARS-CoV-2 testing registries at the sites to conduct additional outreach. Contact information (email and telephone numbers) provided by SARS-CoV-2 positive individuals at the time of testing may be used to recruit eligible participants through IRB approved scripted outreach communications such as phone call or emails. Clinical trial sites may use IRB approved recruitment and retention services for potential SARS-CoV-2-positive individuals and contacts.

SARS-CoV-2 positive individuals will be recruited and screened for enrollment in the early treatment indication (if currently enrolling at the site). The study team will work with the individual to help them recall everyone with whom they have had contact during the timeframe while they may have been infectious. The study team will then reach out to those individuals identified as contacts, either via phone, email or in person, to recruit for study enrollment. To protect participant privacy, contacts are only informed that they may have been exposed to an

individual with the infection. They are not told the identity of the individual who may have exposed them. SARS-CoV-2 positive cases do not need to be enrolled in the early treatment indication of the study to serve as source of contacts for PEP indication (such as children or those who decline enrollment).

Recruitment of household contacts will represent an important source of contact enrollment. Household enrollment will facilitate coordination of testing and follow up for multiple study participants. Adult contacts of positive cases meeting entry criteria will be eligible for enrollment. Recruitment of adult SARS-CoV-2 confirmed study participants residing in institutional care facilities will rely heavily on direct interface of the study team with facility staff. Once an infected resident or facility staff has been confirmed, other adult residents or staff may be recruited.

Clinical trial sites may receive referrals of SARS-CoV-2-positive individuals and their contacts from other local medical facilities. Site team members will engage with relevant facility staff to identify presumptively eligible participants. The study will be described to the individual, and if they are interested, the informed consent will be reviewed with the participant. After signing/acknowledging the screening informed consent, their eligibility to participate will be assessed. For those with confirmed infection in shared or congregate living arrangements, room access may be limited, and consent may be performed by study staff members with participant access.

Compensation for study participation will be provided. The amount and mechanism of compensation will be determined locally and in accordance with local IRB requirements and subject to local IRB approval.

7 STUDY INTERVENTION

Information about the study product(s) can be found in the product specific appendix. Product specific appendices for each investigation product will outline toxicity, side effects, administration procedures, monitoring, and pregnancy/breastfeeding restrictions.

7.1 Study Intervention(s) Administration

Refer to appendix/appendices for details of investigational products.

7.1.1 Study Intervention Description

Refer to appendix/appendices for details of investigational products.

7.1.2 Dosing and Administration

Refer to appendix/appendices for details of investigational products.

7.2 Preparation/Handling/Storage/Accountability

Refer to appendix/appendices for details of investigational products.

7.2.1 Acquisition and Accountability

Refer to appendix/appendices for details of investigational products.

7.2.2 Acquisition

Refer to appendix/appendices for details of investigational products.

7.2.3 Accountability

The site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Time of study drug administration to the participant will be recorded on the appropriate Case Report Form (CRF). All study product(s), whether administered or not, must be documented on the appropriate study product accountability record or dispensing log. The IND Sponsor's monitoring staff will verify the participating site's study product accountability records and dispensing logs per the site monitoring plan.

After the study is completed or terminated return, export, or destruction of unused IP shall occur at the Industry Supporter's written directive.

7.2.4 Formulation, Appearance, Packaging, and Labeling

Refer to appendix/appendices for details of investigational products.

7.2.5 Product Storage and Stability

Refer to appendix/appendices for details of investigational products.

7.2.6 Preparation

Refer to appendix/appendices for details of investigational products.

7.3 Prohibited Medications

Refer to appendix/appendices for details of investigational products.

7.4 Measures to Minimize Bias: Randomization and Blinding

7.4.1 Randomization

Following completion of the screening informed consent and determination of eligibility under that Master Protocol, participants will be stratified as either an eligible SARS-CoV-2 positive case or SARS-CoV-2 negative contact. Once identified as a case or contact, participants will then undergo product specific informed consenting. If eligible to contribute to a shared placebo pool (i.e., participant potentially meets eligibility criteria for more than one PSA), the participant will complete informed consent for all PSAs for which they may be eligible. Following PSA informed consenting, the participant will complete all product specific screening requirements to determine final eligibility for all PSAs for which they may be eligible.

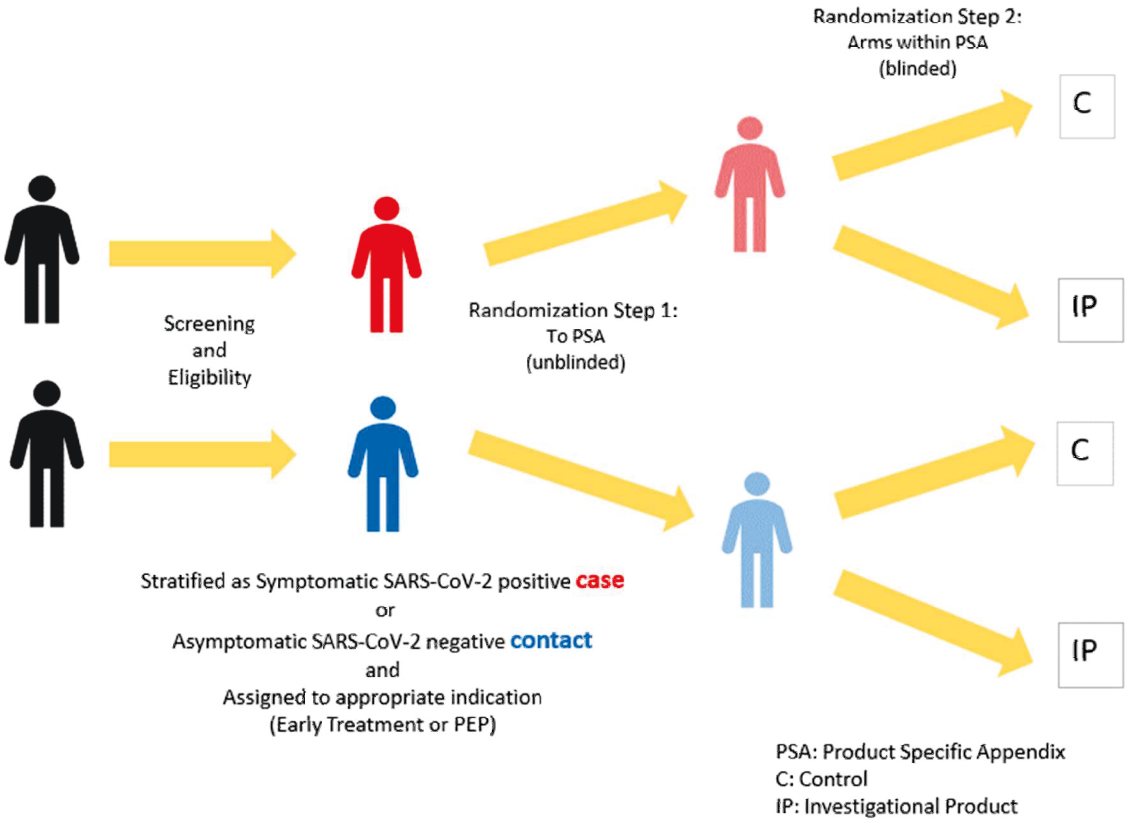
Once PSA eligibility has been determined, the participant will undergo the first randomization to a PSA enrolling in their strata for which they are eligible. Participants must be eligible for at least one PSA enrolling in their strata. Probability of randomization to a PSA for which a participant is eligible will be equally likely to each PSA. For example, if a participant has consented and meets the eligibility criteria for three products enrolling in the PEP indication at the same time, probability of randomization of a contact to one of these PSAs is 1:1:1. The first randomization is unblinded.

Following the first randomization, a second randomization, within each PSA, will be to the arms within the respective PSA. The default is an investigational product or the investigational product's control arm. Probability of randomization will be dependent on the number of PSAs enrolling in the indication at that time which are contributing to a shared placebo pool and for which the participant is eligible. In order to be considered for placebo sharing, the participant must meet product specific eligibility criteria for all PSAs contributing to the shared placebo pool. The ratio of assignment to IP or control would be r:1 where r is the number of PSAs contributing to a shared placebo pool that a given participant is determined to be eligible to receive. For example, if two products are enrolling in the PEP indication simultaneously for which the participant meets the eligibility criteria and are contributing to a shared placebo pool,

the probability of randomization of the participant to IP or placebo would be 2:1. The second randomization is blinded.

Following randomization and double blinded administration of intervention, participants will be monitored with regular physical exams and laboratory tests to assess safety and efficacy. The visit schedule and data collection will be the same within a stratum across the different appendices. Figure 1 outlines the randomization schema.

Figure 1. Participant Stratification and Randomization Plan



The randomization plan for both the Early Treatment and PEP indications are presented in Figure 2 and Figure 3. Figure 2 outlines the randomization scheme if a participant only meets the eligibility criteria for one PSA enrolling in their strata. Figure 3 outlines the randomization scheme if a participant meets the eligibility criteria for two PSAs enrolling in their strata contributing to a shared placebo pool.

Figure 2. Randomization Scheme for Early Treatment and PEP Indications: Participant Eligible for One PSA

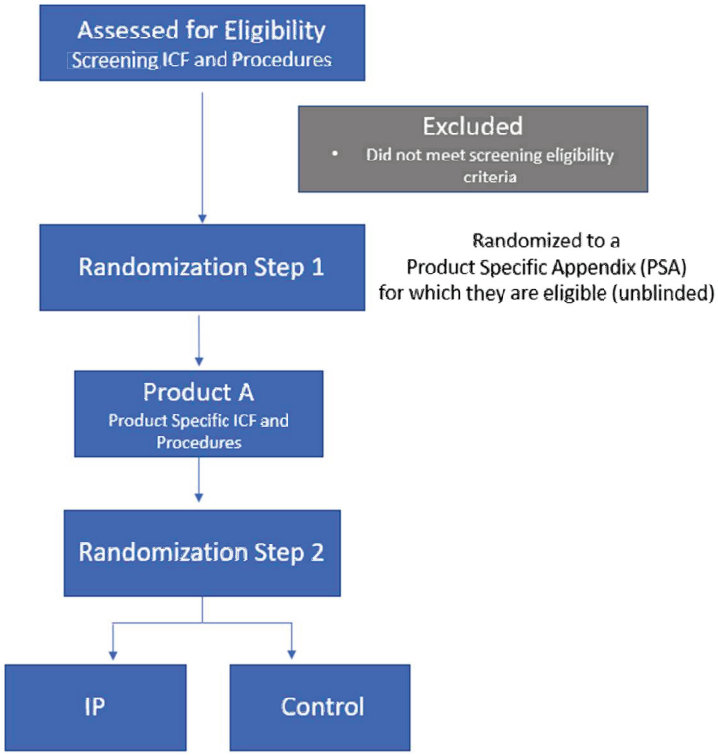
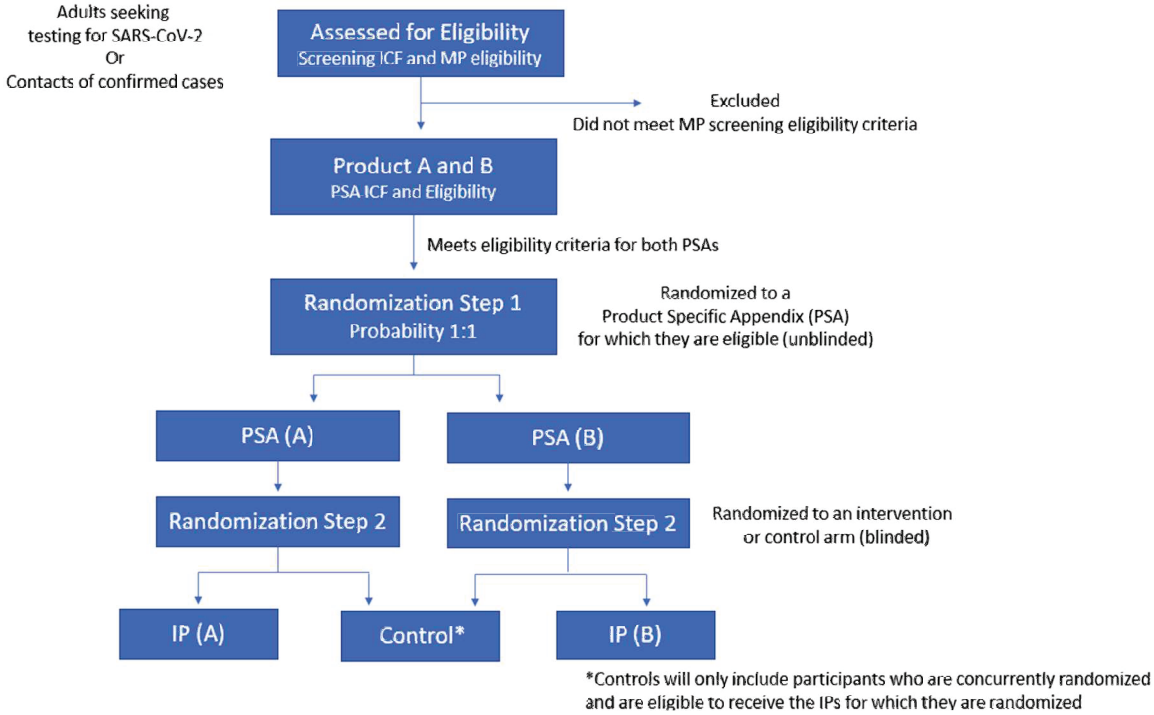


Figure 3. Randomization Scheme for Early Treatment and PEP Indications: Participant Eligible for Two PSAs



7.4.2 Blinding and Unblinding

There will be a two-step randomization process (described above in Section 7.4.1 Randomization). Participants, study staff, and study investigators will not be blinded to the first step, randomization to the PSA. Participants will be randomized to a PSA for which they meet the eligibility criteria, and which are enrolling in their strata. Participants will then be randomized to an arm within their respective PSA. Both participants and study investigators will be blinded to the second randomization. IP delivery methods and packaging will be similar for each arm within a PSA (for example, an intravenously administered IP will have a similar appearing, intravenously administered control).

Randomization to the arm within the respective PSA will be implemented through an Interactive Voice/Web Response System (IxRS) managed by IND Sponsor.

Unblinding will be permitted during the trial in the following events:

- Emergency Unblinding: where knowledge of the treatment randomization is necessary to provide acute medical care or where there is a safety concern by the treating clinician. Details of the unblinding will be captured in the CRF including:
  - Date/timing
  - Reasons for unblinding
  - Name and roles of staff and participants involved in unblinding
  - Required clinical care
  - Event outcome
- To the DSMB for safety monitoring
- Statistical Analysis: unblinded results will be used in the interim and final analyses
- Participant notification: All participants will have the option to learn their randomization assignment after their PSA has been completed

In the event unblinding is required every effort will be made to limit this information to those individuals directly involved in the statistical analysis or care decisions and not with study staff.

7.5 Study Intervention Compliance

To enhance validity of the study data, several methods will be used to assess compliance with the intervention. These will include pill counts, self-reported medication compliance, adherence reminders with each study visit, and feedback investigating reasons for noncompliance. Adherence reminders will take place at each applicable study visit and with the Daily Follow Up Symptom Questionnaire (depending on the dosing schedule of the study drug). Study staff will also review dosing instructions, as well as allow the participant to provide feedback on challenges with study drug compliance.

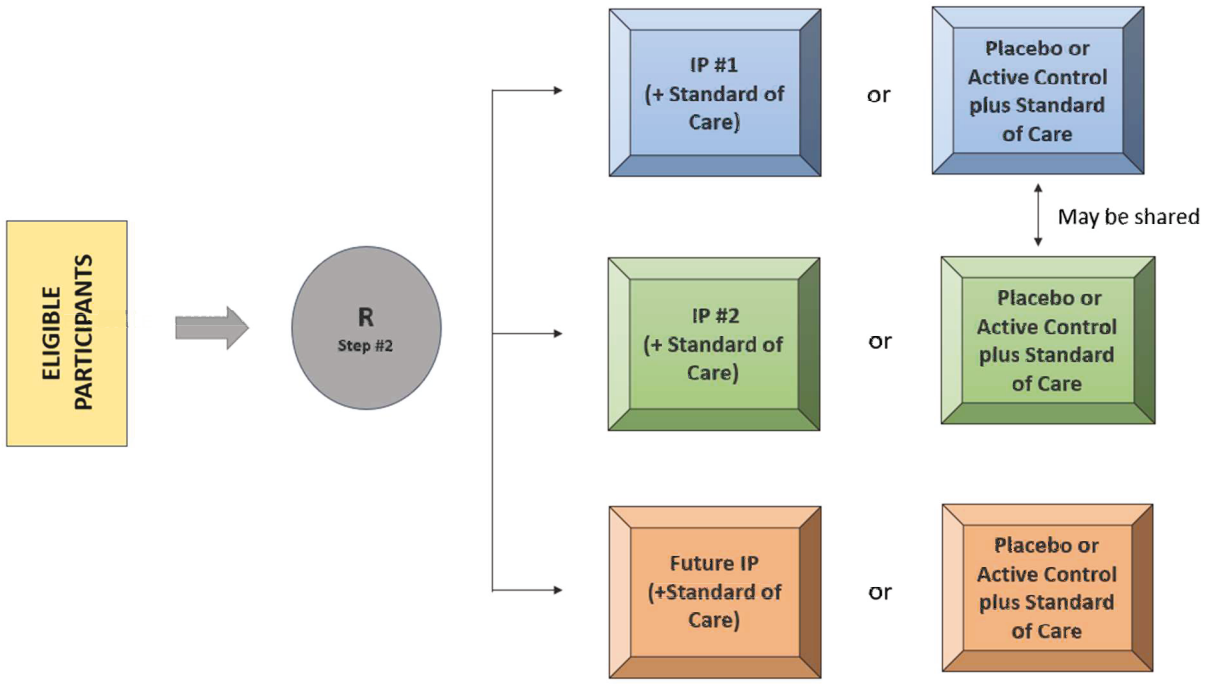
7.6 Concomitant Therapy

Patient-reported medication history during the 30 days prior to ICF signing will be recorded at Screening. Thereafter, any changes in concomitant medications or new medications added will be recorded in the data collection forms. While most systemic medications taken by the subject, other than study drug, are considered concomitant medications and should be recorded, the following specific exceptions do not need to be recorded: topical medications (eye drops, ear drops, intranasal drops or sprays, dermatologic treatments, topical lidocaine). In contrast, the following should be recorded: vitamins and supplements (e.g., vitamins, minerals, herbal supplements, dietary supplements, iron/ferrous sulfate, magnesium, calcium, electrolyte replacements) and nicotine replacement products (e.g., patches, lozenges, gums, nasal sprays).

7.7 Standard of Care

Treatment that experts agree is appropriate, accepted, and widely used and that follows established and approved local treatment algorithms will be allowed in the study. Both placebo control and IP intervention arms will be eligible for receipt of Standard of Care (SOC) treatments and decisions will be based on judgement by the treating clinician. Figure 4 presents the second randomization step outlining the use of IPs in conjunction with SOC.

Figure 4. Second Randomization Step: IPs with SOC Treatment Allocation



The PSA may detail specific exclusion criteria for SOC treatments.

7.7.1 Rescue Medicine

For this protocol, rescue medication is defined as a medication (prescribed or over the counter) for the treatment of SARS-CoV-2 infection, anticipated adverse reactions, and anticipated emergency situations. Use of these medications will be allowed with participation in the protocol. Drug, timing, dose, and frequency of rescue medications will be reported in the CRF.

8 PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Participants will be informed that participation is voluntary and that they may withdraw from the study or discontinue the IP at any time, without prejudice upon request. Discontinuation of the investigational product does not mean discontinuation from the study. When a participant's withdrawal request is limited to discontinuation of the IP, other activities outlined in the schedule of activities for which the participant previously gave consent may continue. The study staff will clarify whether the participant wishes to withdraw from all components of the trial or only from the IP.

8.1 Participant Discontinuation of IP

A participant may discontinue IP at their request for any reason. Every effort should be made to encourage subjects to remain in the study for the duration of their planned outcome assessments. Unless the subject withdraws the consent, those who discontinue study drug early will remain in the study. The reason for subject IP discontinuation will be documented in the case report form. If a participant discontinues the IP, data collection, both clinical and lab, for which the participant consents will continue as per the schedule of activities.

An investigator, in consultation with the medical monitor, may discontinue IP administration for a participant in the study for the following reasons:

- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

8.2 Withdrawal of Consent

Participants who request to discontinue receipt of the IP will remain in the study and will continue to be followed for protocol specified follow up procedures. The only exception to this is when a participant specifically withdraws consent for participation in any further study activities and further contact from study staff. Participants should notify the investigator in writing of the decision to withdraw consent from future follow up, whenever possible. Participants may also continue or revoke consent for access to health information for the purpose of the research study. Revoking access to health information will require a written notification from the participant.

If a participant withdraws fully from the study and does not consent to continued follow-up of associated clinical and laboratory data, then the active collection of participant study data ends when consent is withdrawn. The IND Sponsor may retain and continue to use any data collected before withdrawal of consent.

Although a participant is not obligated to give reason(s) for withdrawal from a trial, the site investigator will make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. Reasons for withdrawal, if obtained, will be entered into the CRF.

8.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she is unable to be contacted by the clinical trial site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within the visit window and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Periodic attempts will be made to contact subjects who are noncompliant with study visits and study activities
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's research record or study file.
- Should the participant continue to be unreachable, he or she will be considered lost to follow up
- Should a participant be hospitalized during their time on-study, efforts will be made to collect study data and clinical specimens in accordance with the study Schedule of Activities where possible.

Participants who withdraw from the study or are lost to follow up after signing the ICF and administration of the IP will not be replaced.

9 STUDY ASSESSMENTS AND PROCEDURES

The study assessments are outlined in Section 1.2 Schedule of Activities (SoA).

Every effort will be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that, from time to time, there may be circumstances, outside of the control of the investigator, that make it not feasible to perform the activity. In these cases, the investigator will take all steps necessary to ensure the safety and wellbeing of the participant. If the participant is not able to complete the activities during this timeframe, the visit and associated activities may still take place; the visit will be identified as a protocol deviation and captured in the appropriate CRF. If the visit is not completed, the participant may continue to be enrolled in the study and proceed with the subsequent schedule of activities; incomplete visits will be captured in the appropriate CRF. When a protocol required assessment cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he/she has taken/will take to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

9.1 Efficacy Assessments

The key efficacy assessment in the early treatment indication is time to sustained alleviation or resolution of symptoms among SARS-CoV-2 positive cases. Time to sustained alleviation or resolution of targeted COVID-19 symptoms (listed in Supplement 3) will be defined as the number of days from randomization in a PSA (Step 2 of randomization) to the first day the participant reports all symptoms as mild or none (≤ 1 on the Daily Follow Up Symptom Questionnaire) for at least 3 consecutive days (the first day being considered the Event Day).

The key efficacy assessment in post-exposure prophylaxis is incidence of COVID-19 infection defined as positive RT-PCR test and presence of at least one COVID-19 symptom.

9.2 Clinical and Laboratory Assessments

Study procedures are specified in Section 1.2 Schedule of Activities (SoA).

9.2.1 Clinical Assessments

Clinical assessments include:

Vital Signs

Temperature, pulse, blood pressure, respiratory rate, and pulse oximetry.

Physical Exam

Performance and documentation of an exam that evaluates the following systems: General, Head Eyes Ear Nose and Throat, Pulmonary, Cardiac, Abdomen, Neurologic, Extremities, and Skin.

Symptom Review: Screening Symptoms Questionnaire and Daily Follow Up Symptom Questionnaire

Participants will complete two symptom questionnaires during their time in the study: the Screening Symptoms Questionnaire and the Daily Follow Up Symptom Questionnaire (Supplements 1&2) adapted from the US Food and Drug Administration (FDA) guidance [Guidance for Industry]. Prior to use in the study, the symptom questionnaires will be certified translated and back translated with comparisons of the original language version and the back translated version. Pilot testing of the questionnaires will be conducted among individuals whose language is the translated language of the instrument to evaluate the instructions, response format and the items in the instrument for clarity.

The Screening Symptom Questionnaire (Supplement 1) will be completed at Screening and Enrollment (Day 0). If Screening and Enrollment visits are completed on the same day, Screening Questionnaire will be completed once. If Screening and Enrollment visits are completed on separate days, Screening Questionnaire will be completed on both days. The Screening Questionnaire will be used to establish baseline symptoms and study eligibility. The questionnaire will also ascertain pre-COVID-19 illness screening symptom levels.

Participants will complete Daily Symptom Follow Up Questionnaire (Supplement 2) on Days 1 through 28 and then at follow up visits. Participants will have the option to complete the questionnaire on their personal computer or personal smart device, or on paper. For participants completing the questionnaire electronically, paper forms will be provided as back up. Paper forms will be entered into the clinical database by research staff. Participants will be encouraged to use the same method (email, personal smart device, or paper) throughout their study participation.

Several methods will be used to assess compliance with the intervention. These will include pill counts, self-reported medication compliance, adherence reminders with each study visit, and feedback investigating reasons for noncompliance. Daily reminders will be sent via text, email, or phone call on Days 1 through 28. Adherence reminders will also take place at each applicable study visit and with the Daily Follow Up Symptom Questionnaire (depending on the dosing schedule of the study drug). Study staff will also review dosing instructions, as well as allow the participant to provide feedback on challenges with study drug compliance.

Study staff may also provide the questionnaire in an interview format (in person or remotely) to the participant and input verbal responses from the participant into the clinical database or on paper for participants who are unable to complete the questionnaire (ex. illiterate participants or other inability to complete an electronic or paper format). The format in which the questionnaire was completed (self-evaluation vs interview format) will be recorded.

Symptoms elicited in the Daily Symptom Follow Up Questionnaire are outlined in Supplement 2 and include nasal congestion, sore throat, hoarse voice, shortness of breath, cough, fatigue, myalgias, headache, chills, fever, nausea or vomiting, change in taste and change in smell. Symptoms will be reported on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). Additional questions will assess overall symptom severity (on the 4-point scale), return to health,

and return to usual activities. The questionnaire will also ascertain the presence of any new symptoms not elicited in the questionnaire.

Medication Review

Self-reported medication use including prescription, traditional medicines, and nonprescription medications. Reporting will inquire about indication, symptom(s) being addressed, frequency, dosing, and duration of use.

Medical History

Reviewed by research staff with participant. Documentation of comorbidities (identifying current diagnoses or history of condition) and other lifestyle factors including:

- Cardiac arrhythmia
- Ischemic health disease
- Peripheral vascular disease
- Venous thromboembolism
- Diabetes (insulin dependent or non-insulin dependent)
- Human Immunodeficiency Virus (HIV)
- Asthma
- Chronic obstructive pulmonary disease (COPD)
- Chronic Kidney Disease (dialysis dependent or not on dialysis)
- Liver Disease
- Hypertension
- Cancer (solid tumor)
- Cancer (hematologic)
- Immunosuppressive conditions or Chronic immunosuppressant use
- Obesity (defined as body mass index [BMI] >30; may be based on self-report or calculation from height and weight)
- Dementia or other chronic neurologic condition
- Smoking/Vaping
- Severe genetic or developmental disabilities
- Sickle cell disease or thalassemia
- Solid or hematologic organ transplant
- Tuberculosis

Clinical Outcome

Medical chart abstraction will be performed if participant seeks additional care, is hospitalized, or for unanticipated visits.

Clinical data collection from the healthcare encounter will capture:

- Date and timing of clinical care
- Clinical presentation
- Clinical care delivered
- Results of diagnostic testing
- Medication administration
- Response to treatment
- Clinical outcome

Vaccination status

Vaccine manufacturer and date of each dose if recalled by the participant.

Adverse Events

Participants will be assessed at every visit for any new symptoms or additional care sought and their relationship to the study intervention. Participants will also be provided contact information to report any of these new symptoms or healthcare visits to research staff between visits. See Section 10.3 Methods for Obtaining Adverse Event and Serious Adverse Event Data.

9.2.2 Lab Assessments

The following laboratory evaluations are for all investigational products:

Hematology

Complete blood count: white blood cell count with differential, hemoglobin, hematocrit, platelet count measured using Abbot CellDyn® Hematology Analyzer or similar equipment.

Refer to PSA for additional testing requirements.

Chemistry

Serum: sodium, potassium, chloride, CO_2, glucose, BUN, creatinine, calculated eGFR, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin, direct bilirubin, and total protein using Piccolo® General Chemistry 13 or similar equipment.

Refer to PSA for additional testing requirements.

Pregnancy Testing

Pregnancy testing will be completed at screening and any time pregnancy is suspected. Pregnancy testing will be completed in all females of childbearing potential defined as

premenopausal females capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception and women whose male sexual partners have been vasectomized or are using contraceptive devices. For females of childbearing potential, negative serum or urine pregnancy test will be completed at or within 24 hours prior to study enrollment by any clinic or laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or by a point of care (POC)/CLIA-waived test.

In the event of pregnancy occurring during the study, pregnancy and pregnancy outcome will be reported. See Section 10.1.9 Reporting of Pregnancy and Breastfeeding.

Refer to PSA for additional pregnancy testing requirements.

SARS-CoV-2 Testing

Diagnostic testing must be an approved molecular or antigen diagnostic test for SARS-CoV-2 from any upper respiratory specimen. The test used must be authorized for use by the relevant national authority for the detection of SARS-CoV-2 in the country where the test is administered. Historical testing results will be acceptable if testing performed within the required window (within 24 hours of enrollment for post-exposure prophylaxis and within 5 days of enrollment for early treatment) and the verified result can be presented to the research staff at screening. The local testing result, specimen type, assay type, and date of test will be recorded in the CRF.

For efficacy assessments, nasal swabs will be collected for SARS- CoV-2 ribonucleic acid (RNA). A core laboratory will be used for the performance of all study testing. Qualitative and quantitative PCR will use the Abbott RealTi*m*e SARS-CoV-2 RT-PCR assay on the M200 platform and ThermoFisher assays which have been authorized for emergency use by FDA under an EUA for use by authorized laboratories. Viral sequencing will be performed using the Ion Ampliseq™ SARS-CoV-2 research panel on the Genexus instrument, for research use only.

Remote sampling will utilize the Zymo Research Corporation Swab Collection Kit or similar for extracting and purifying RNA. The kit contains a sonication medium to maintain the integrity of the RNA, while disrupting cells and dissolving cell components. RNA can remain stable in a specimen for up to 30 days at room temperature.

For self-collected specimens, participants will first be instructed on proper self-collection technique and be provided a pictorial instruction guide.

9.2.3 Screening Assessments

For the MP, screening assessment include:

- SARS-CoV-2 diagnostic testing
- SARS-CoV-2 vaccination status
- Concomitant medications
- Pregnancy testing
- Screening symptom questionnaire

PSAs will detail any additional product specific screening assessment requirements. Final eligibility will be determined by the site PI after review of all screening assessments.

9.2.4 Stored Specimens

With participant consent, collected upper respiratory specimens, plasma, sera, or nucleic acid stabilized whole blood (or whole blood) will be collected and may be used to assess SARS-CoV-2 virologic and immune responses. All Entry/Day 0 specimens should be collected prior to the first dose of IP or placebo. Specimens will be stored indefinitely, or until none is left for use.

Stored Whole Blood

Stored whole blood and nucleic acid stabilized whole blood will be collected and stored for future testing which may include:

- Immunologic host-response studies
- Host transcriptomics analysis

Stored Plasma

Blood plasma will be collected and stored for future testing which may include:

- Immunologic host-response studies
- SARS-CoV-2 seroconversion and antibody titers (among seroconverters)
- Quantitative SARS-CoV-2 RNA

Stored Serum

Blood sera will be collected and stored for future testing which may include:

- Total and neutralizing antibody assays
- Immunologic host-response studies

Stored Upper Respiratory Specimens

Upper respiratory specimens will be collected and stored for future testing which may include:

- Quantitative and qualitative SARS-CoV-2 RNA
- Quantitative and qualitative influenza-like illness respiratory pathogen RNA
- SARS-CoV-2 variant identification

Additional specimens will be collected for product-specific evaluations per the PSAs.

9.2.5 Blood Volumes

Product specific study assessments, specimen collection schedules and specimen volumes will be outlined in the product specific appendices.

9.2.6 Pharmacokinetics

Refer to PSA

9.3 Procedures to Follow in the Event of Abnormal Laboratory Test Values or Clinical Findings

Abnormal findings from clinical or laboratory assessments will be evaluated for clinical significance throughout the trial. If a test is deemed to be clinically significant, it may be repeated, for verification. If a test remains clinically significant, the participant will be informed of the results and the appropriate medical care or follow up will be arranged with the permission of the participant. Decisions to exclude the participant from enrolling in the trial or withdraw the participant from the trial will be at the discretion of the site principal investigator (PI) in coordination with the medical monitor. Laboratory adverse events will be recorded in the appropriate CRF.

9.4 Study Visits

9.4.1 Screening Visit - In Person or Remote (Within 24 hours prior to Enrollment)

Potential participants will be screened for presumptive eligibility for the study according to the procedures described below. All procedures may be completed in a stepwise manner, as suggested below, for potential participants who meet the study eligibility criteria. For participants who do not meet the eligibility criteria, screening will be discontinued when ineligibility is determined. For potential participants who participate in the screening visit **remotely** and are found to be presumptively eligible, final eligibility will be confirmed upon completion of screening procedures at the Enrollment Visit scheduled to take place within 24 hours of screening. Screening and enrollment may take place on the same day (Day 0).

- Screening Informed Consent (in person or verbal (See Section 14.1.2 Informed Consent Process)
- Screening Symptom Questionnaire
- Demographics
- Medical History
- Physical Exam
- Vital Signs
- Height and Weight
- SARS-CoV-2 Vaccination Status
- Diagnostic Test for SARS-CoV-2 (for eligibility assessment)
- Pregnancy test for women of childbearing potential
- Concomitant medication review

9.4.2 Enrollment Visit – In Person (Day 0)

Participants who are found to be presumptively eligible at their Screening Visit will complete the Enrollment visit within 24 hours of the Screening Visit. Participants who completed the screening visit remotely will complete all remaining screening procedures as well as enrollment procedures during the in-person Enrollment Visit. Participants who do not complete an Enrollment Visit within 24 hours of screening must repeat the entire Screening Visit. All participants must complete the screening evaluation prior to study enrollment. For those who meet the study eligibility criteria from the screening procedures, the enrollment procedures below may be undertaken in a stepwise manner, as suggested below, to confirm eligibility. As done with the Screening Visit, procedures will be discontinued if ineligibility is determined at this visit. The site investigator will review all screening assessments (physical exam, medical history, laboratories etc.) prior to product administration to determine final eligibility for the PSA to which the participant has been randomized

- Screening Symptom Questionnaire (repeat if visit not performed on same day as Screening)
- PSA (IP) Informed Consent (in person) (for all PSAs for which the participant may be eligible and are contributing to a shared placebo pool)
- PSA screening assessments (for all PSAs for which the participant may be eligible, completed informed consent, and are contributing to a shared placebo pool)
- Randomization (Step 1) (upon completion and review of all MP and PSA screening assessments by the site PI)
- Randomization (Step 2)
- Vital Signs
- Upper Respiratory Specimen Collection (prior to administration of IP or control)
- Venous Blood Sampling (prior to administration of IP or control)
- Administer IP or Control (Refer to PSA)
- Dispense Study Kit
- Collect and Update Contacts
- Adverse Event Recording and Reporting

9.4.3 Day 3 – Remote or In Person

This visit is scheduled to take remotely or in person on Day 3. Every effort should be made to complete the Day 3 visit requirements on Day 3; however, the visit may take place - if necessary +/- 1 days. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person

If conducted remotely the following procedures will be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Collect and Update Contacts
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection (self-collection)
- Clinical Outcome Assessment
- Adverse Event Recording and Reporting

If conducted in person following procedures will be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Collect and Update Contacts
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection
- Clinical Outcome Assessment
- Vital Signs
- Physical Exam
- Venous Blood Sampling
- Adverse Event Recording and Reporting

9.4.4 Day 7 – Remote or In Person

This visit is scheduled to take place in person or remotely on Day 7. Every effort should be made to complete the Day 7 visit requirements on Day 7; however, the visit may take place — if necessary +/- 1 days. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person

If conducted remotely the following procedures will be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Collect and Update Contacts
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection (self-collection)
- Clinical Outcome Assessment
- Adverse Event Recording and Reporting

If conducted in person following procedures will be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Collect and Update Contacts
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection
- Clinical Outcome Assessment
- Vital Signs
- Physical Exam
- Venous Blood Sampling
- Adverse Event Recording and Reporting

9.4.5 Day 10 – Remote

This visit is scheduled to take place remotely on Day 10. Every effort should be made to complete the Day 10 visit requirements on Day 10; however, the visit may take place — if necessary +/- 1 days. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person

- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Concomitant medication review
- Clinical outcome assessment
- Upper Respiratory Specimen Collection (self-collection)
- Adverse Event Recording and Reporting

9.4.6 Day 14 – In Person

This visit is scheduled to take place on Day 14. Every effort should be made to complete the Day 14 visit requirements on Day 14; however, the visit may take place — if necessary +/- 2 days.

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection
- Clinical Outcome Assessment
- Vital Signs
- Physical Exam
- Venous Blood Sampling
- Adverse Event Recording and Reporting

9.4.7 Day 28 – In Person

This visit is scheduled to take place on Day 28. Every effort should be made to complete the Day 28 visit requirements on Day 28; however, the visit may take place — if necessary +/- 4 days.

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection
- Clinical Outcome Assessment

- Vital Signs
- Physical Exam
- Venous Blood Sampling
- Adverse Event Recording and Reporting

9.4.8 Week 12 – In Person or Remote

This visit is scheduled to take place at Week 12. The visit may be conducted in person or remotely. Every effort should be made to complete the Week 12 visit requirements at Week 12; however, the visit may take place - if necessary +/- 2 weeks. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person

If conducted remotely the following procedures will be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection (self-collection)
- Clinical Outcome Assessment
- Adverse Event Recording and Reporting

If conducted in person following procedures will be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Daily Follow Up Symptom Questionnaire (Day 1 until Day 28 then at Week 12)
- Upper Respiratory Specimen Collection
- Clinical Outcome Assessment
- Vital Signs
- Physical Exam
- Venous Blood Sampling
- Adverse Event Recording and Reporting

9.4.9 Unscheduled Visits – In Person or Remote

An unscheduled visit is defined as any visit to the clinical trial site outside of the protocol evaluation time points, where the participant is seen by a member of the clinical research staff. Participants will be encouraged to report any medical problems or discomfort to the study staff and may be instructed to return to the clinical trial site if they experience new or worsening COVID-19 symptoms or become infected with SARS-CoV-2 any time after enrollment. Remote visits may include visits by the study staff to the participant or via phone/video conference. If remote visit not feasible or is not permissible under local rules or standards, the visit may be conducted in person.

In the event of an unscheduled visit these procedures may be done according to clinical judgement:

If conducted remotely the following procedures may be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Daily Follow Up Symptom Questionnaire
- Upper Respiratory Specimen Collection (self-collection)
- Clinical Outcome Assessment
- Adverse Event Recording and Reporting

If conducted in person following procedures may be performed:

- SARS-CoV-2 Vaccination Status
- Concomitant Medication Review
- Daily Follow Up Symptom Questionnaire
- Upper Respiratory Specimen Collection
- Clinical Outcome Assessment
- Vital Signs
- Physical Exam
- Venous Blood Sampling
- Adverse Event Recording and Reporting

Depending on the reason for the visit, the participant may have additional assessments or laboratory tests, as clinically indicated, or may be referred to the appropriate service for follow up.

9.4.10 Worsening/Hospitalization

In the event a participant is worsened and requires other SOC treatment or hospitalization during the course of the study, IP administration will be discontinued. Participant will continue to be followed and will not be withdrawn from the study. If possible, schedule of activities will continue during hospitalization. If unable to complete study activities during hospitalization, study procedures may resume after discharge. Consent may be obtained from the participant to access hospital or autopsy records.

Clinical data collection from the healthcare encounter will capture the following (when possible):

- Date and timing of clinical care
- Clinical presentation
- Clinical care delivered
- Results of diagnostic testing
- Medication administration
- Response to treatment
- Clinical outcome
- Clinical specimen remnants (if available)

10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

10.1 Definition of Adverse Events (AE)

An adverse event is any untoward medical occurrence associated with the use of an intervention in humans, regardless if considered intervention-related or not. All adverse events that occur from the first dose of study medication through Week 12 after enrollment must be recorded. All changes in health statuses documented by participants must be reviewed by sites to determine if it qualifies as an AE. To formally document the AE, the site must complete an Adverse Event report.

10.1.1 Definition of Treatment Emergent Adverse Events

A treatment-emergent adverse event is defined as any event not present prior to the initiation of the IP or any event already present that worsens in either intensity or frequency following exposure to the IP.

10.1.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator, medical monitor, or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.1.3 Classification of Adverse Events

Adverse events can be classified as/by:

- DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) corrected Version 2.1, July 2017 [DAIDS]
- Investigational Product or Study Participation related or not Investigational Product or Study Participation related

- Severity of Event

To maintain accuracy and consistency in the evaluation of AEs, study staff will be trained on and utilize the National Institutes of Health, Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), corrected Version 2.1, July 2017 for reporting of adverse events.

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Grade 1 (Mild) – Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated.
- Grade 2 (Moderate) – Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
- Grade 3 (Severe) – Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated.
- Grade 4 (Life-threatening) – Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability
- Grade 5 (Death)

10.1.4 Relationship to Investigational Product or Study Participation

All adverse events (AEs) must have their relationship to IP or study procedure assessed by the site PI who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study procedure, there is a reasonable possibility that the IP or study participation caused the AE, or there is a temporal relationship between the IP administration or study participation and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IP administration or study participation and the AE.
- **Not Related** – There is not a reasonable possibility that the IP or study participation caused the event, there is no temporal relationship between IP administration or study participation and event onset, or an alternate etiology has been established.

10.1.5 Serious and Unexpected Suspected Adverse Reactions (SUSAR)

In addition to meeting the Serious definition in Section 10.1.2, a Serious and Unexpected Suspected Adverse Reaction (SUSAR) is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed. Following notification from the site PI or appropriate sub-investigator, the sponsor will report any SUSAR in an IND safety report to the FDA and will notify the sites as soon as possible.

10.1.6 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. At each study visit, the investigator will inquire about the occurrence of AEs since the last visit. All AEs occurring while participating in study must be documented appropriately regardless of relationship. All AEs will be followed until resolution or stabilization.

10.1.7 Adverse Event Recording

Adverse events will be recorded using the appropriate CRF. Information to be collected includes the following:

- Event description
- IP (treatment/control) – including administration route and dose
- Time of onset
- Clinician's assessment of severity and relationship to IP or study participation (assessed only by those with the training and authority to make a diagnosis)
- Time of resolution/stabilization of the event - all AEs occurring while participating in study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.
- Additional treatment or stabilization details
- Outcome

10.1.8 Adverse Events of Special Interest

Refer to PSAs for AEs of special interest for specific investigational agents.

10.1.9 Reporting of Pregnancy and Breastfeeding

The use of IPs in pregnancy and breastfeeding will vary depending upon IP. The ability to continue or need to discontinue IP in the event of pregnancy or breastfeeding is outlined in the relevant appendix/appendices.

If a participant becomes pregnant during the study (post enrollment), study follow up will continue for the duration of the study. At the end of the pregnancy, outcome and adverse events for participant and infant will be recorded on the outcome CRF.

10.1.10 Serious Adverse Event Reporting

All SAEs will be reported to the sponsor and country regulatory agencies independent of its relatedness to the use of Investigational Product (IP). US sites and Country sites will be responsible to report SAEs to the IND Sponsor up to 24 hours of awareness of the event and, to

follow up on those events up to resolution and/or once an outcome is reached. Initial and Follow up SAE reports are mandatory.

Any event that requires expedited reporting to Regulatory Authorities (i.e., Serious Unexpected Suspected Adverse Reactions [SUSARs]) based on applicable national regulations will be forwarded to the IND sponsor in time to meet reporting requirements (e.g., 7 days for fatal and life-threatening initial reports, with follow up reports within another 8 days, 15 days for all other SUSARs). The IND sponsor or its in-country representative will submit safety reports (e.g., IND safety reports) to the regulatory agencies as necessary and will inform the investigators of such regulatory reports. Site investigators must submit safety reports as required by their IRB. Documentation of the submission and receipt by the IRB must be retained for each expedited safety report.

Other supporting documentation of the event may be requested by the Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. (HJF) or the IND sponsor and should be provided as soon as possible. The Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study participant safety and protocol conduct.

The IND sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the IND sponsor's initial receipt of the information. In addition, the IND sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

At any time after completion of the study, if the site PI or appropriate sub-investigator becomes aware of an SAE that occurred during the participant's participation in the trial, the site PI or appropriate sub investigator will report the event to the IND sponsor. The IND Sponsor will report SAEs that are not SUSARs to the FDA at least annually in a summary format which includes all SAEs.

AEs, SAEs and SUSARs will be reported to the Central IRB (Advarra) or the local IRB of record in accordance with the IRB's (Advarra or local) defined requirements and timelines. Sites may have additional local reporting requirements (to national regulatory authority).

10.2 Unanticipated Problems

10.2.1 Definition of Unanticipated Problems (UP)

Unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given
  - the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and
  - the characteristics of the participant population being studied.
- Related to the IP or study participation; and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.2.2 Unanticipated Problem Reporting

AEs that are not serious but that are notable and could involve risks to participants will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

The UP report will include the following information:

- Study identifying information: protocol title and number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.

10.3 Methods for Obtaining Adverse Event and Serious Adverse Event Data

Adverse events will be assessed starting at Day 0 through study completion or discontinuation. At every study visit, participants will be asked open ended questions to elicit any changes in their well-being. They will also be asked if they have had to seek additional medical care or testing, been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications). Results will be recorded in the appropriate AE CRF

If the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the investigational agent or study participation, the investigator must promptly notify the sponsor. Serious AEs that occur after study completion or discontinuation need not be reported unless the investigator considers them related to the investigational product.

In addition to participant observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, or identified from review of other documents that are relevant to participant safety will be documented in the AE CRF.

The investigator (and/or any designees) and medical monitor are responsible for detecting, documenting, and reporting events that meet the definition of an adverse event or serious adverse event and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or the study.

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator in conjunction with the medical monitor to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.

10.4 Serious Adverse Event Follow-up

After the initial/serious adverse event report, the investigator in consultation with the medical monitor will proactively follow each participant at subsequent visits or contacts via phone or in person. All serious adverse events, and events of special interest, if applicable, will be followed until resolution, even if this extends beyond the prescribed reporting period. Resolution is the return to baseline status or stabilization of the condition with the probability that it will become chronic. The serious adverse event outcomes will be reported to the IND Sponsor using the appropriate CRF. The investigator and/or medical monitor will submit any updated serious adverse event data to the IND Sponsor within 24 hours of receipt of the information.

If a participant dies during participation in the study the investigator will need to provide a copy of any post-mortem findings, including histopathology, if available.

Investigators are not obligated to actively seek serious adverse events in former participants; however, if a serious adverse event that is considered to be related to the IP occurs in a former participant and is brought to the attention of the investigator at any time following completion of the study, the event will be reported to the Sponsor’s representative.

11 SAFETY AND DATA MONITORING

11.1 Medical Monitor

A medical monitor, representing the IND Sponsor, will be responsible for overseeing the safety and protection of the participants in the trial. The medical monitor will be available at all times and designate a backup if unavailable. Medical monitor will work closely with the Principal Investigator and site PIs and may assist with any of the following:

- Clarification of Inclusion/Exclusion criteria
- Participant concerns
- Adverse events (AEs), Serious adverse events (SAEs), Suspected Unexpected Serious Adverse Reactions (SUSARs)
- Medication errors
- Concomitant medications
- Abnormal laboratory values
- Protocol deviations and waivers
- Unblinding
- Early termination or withdraw of a subject
- Protocol-stopping rules

The medical monitor will document and store all relevant communications in a secure database.

11.2 Protocol Safety Review Team (PSRT)

The PSRT will meet on a regular basis and on an ad hoc basis, as needed. The PSRT will review screening and enrollment summaries, product administration summaries, adverse events, and protocol deviations. The PSRT will also review study operations including regulatory, data management, and pharmacy. On an expedited bases, the PSRT will review all safety events that potentially meet study pause criteria and will decide whether study IP administration should be paused for participant safety purposes. The PSRT may pause IP administration at any time but will use the study pause criteria listed in Section 12.2 Study and/or PSA Pause and Stopping Criteria as a guide. The PSRT may prompt the DSMB to convene to review the events that led to a study pause and make the decision to resume, amend or close the study. IP administration will resume only if PSRT and DSMB reviews of the events that led to the pause result in a recommendation to permit further study IP administration. The IRBs will be notified of the decisions taken by the PSRT and DSMB if they involve suspensions, clinical holds (voluntary or involuntary), or terminations of this research. The PSRT will include the following:

- Medical Monitor
- Study Chair or designee
- Study PI or designees

- IND Sponsor Representative or designee
- Industry supporter representative or designee

Additional PSRT participants may also include the following, as needed:

- Site PIs
- Sub Investigators
- Clinical research nursing staff
- Laboratory staff
- Data management staff
- Regulatory staff

PSRT review via teleconference calls, in-person meetings, or e-mail communications will require, at minimum, the participation of the Medical Monitor, the Study Chair or designee, and the Study PI or designee.

11.3 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be appointed by the IND Sponsor and will consist of a panel of experts who will review the safety and efficacy data for the trial. The DSMB charter will define the responsibilities of the DSMB, detail membership requirements, describe the data to be reviewed, delineate the meeting process, and outline the considerations and policies of the DSMB. Additional details on the DSMB will be provided in the DSMB Charter.

The DSMB may be consulted by the PSRT to review blinded and unblinded data to provide a recommendation on continuing enrollment if there are any questions regarding safety. The DSMB will convene at least every 6 months and/or at the interim triggers (whichever occurs first) to help ensure the safety of the participants in the study. The DSMB will provide recommendations to the study including termination or modification for safety reasons or if there is persuasive evidence of superiority or inferiority of the IP versus the control in its effect on the primary and secondary outcomes. The DSMB may also recommend termination or modification of the MP or PSA if it appears futile on statistical or operational grounds to continue as designed. The DSMB will review the completeness of the study data collected, the adherence to the protocol, safety, and efficacy data. Unless a study pause has been implemented, study activities will continue while awaiting DSMB review.

If there are no safety concerns, the DSMB may recommend continued enrollment of participants pending any interim analyses detailed in the PSA. The DSMB will provide the Study Chair, the Study PI, the site PIs, and the IND Sponsor with any recommendations stemming from the reviews. The IND Sponsor will inform the reviewing IRBs and the FDA of the DSMB recommendations, as needed.

12 PAUSE AND STOPPING CRITERIA

12.1 Individual Participant Pause and Stopping Criteria

The administration of IP to any participant may be stopped or paused for any SAE, clinically significant AE, severe lab abnormality or any medical condition that may indicate to the Investigator or medical monitor that IP continuation is not in the best interest of the participant.

In addition, IP administration will be stopped or paused for the following:

- The subject worsens and requires treatment for worsening COVID-19 as recommended by the NIH [COVID-19 Treatment Guidelines]. All other study activities will continue, participant will not be withdrawn from the study.
- The subject worsens and requires hospitalization for worsening COVID-19. All other study activities will continue, participant will not be withdrawn from the study. Refer to Section 9.4.10 Worsening/Hospitalization

Refer to PSA for additional individual participant pause and stopping criteria

12.2 Study and/or PSA Pause and Stopping Criteria

If one of the PSAs is placed on safety pause, all enrollment and IP administration will be suspended in that PSA until further notice. Study visits will continue. Enrollment and IP administration will resume if and when safety is ensured as determined by the PSRT and medical monitor.

Table 1 summarizes the AEs, which when experienced by at least one participant will lead to a safety pause or prompt PSRT (and DSMB, as applicable) AE review.

- Any Grade 5 event, Grade 4 event, or any Grade 3 hypersensitivity reaction should be reported immediately (within hours of the site learning of the event). These events require prompt review by the PSRT (and/or DSMB as applicable). These events require an immediate study pause.
- Other Grade 3 events that are judged related to IP administration should be reported promptly (within 24 hours of the site learning of the event). These events require prompt review by the PSRT (and DSMB as applicable) for a decision if a study pause is necessary.
- Grade 3 events in two or more participants that are judged related to IP administration from the same system organ class should be reported promptly (within 24 hours of the site learning of the event). These events require prompt review by the PSRT (and DSMB as applicable) for a decision if a study pause is necessary.

Table 1. Adverse Event Notification and Study Pausing Guidelines

Adverse Event	Action [a]
Grade 5/Grade 4 (Or Grade 3 Hypersensitivity) [b]	Automatic pause Immediate reporting (Concurrent with observation or report)
Grade 3 (Other) Related [b]	Consider pause Prompt reporting (within 24 hours of observation or report)

a: Follow-Up and Resolution: All promptly or immediately reportable AEs are followed until resolution or condition is medically stable

b: Laboratory abnormalities must be verified. Verified definition: If no evidence of disease is present other than the abnormal laboratory value, the test must be repeated at least one time in order to be considered "verified". The verification period will be a maximum of 48 hours after initial awareness of the abnormal laboratory value. When signs and symptoms are present, repeat test WILL NOT be needed

For events in the table above, the site PI notifies the PSRT within the time outlined in Table 1 after the site observes or is notified of the AE. The PSRT will convene within one business day to review these adverse events and determine disposition (including whether the DSMB needs to review the event). Refer to PSA for additional study and/or PSA pause and stopping criteria.

12.3 Resumption of Paused Study

If a decision to resume study enrollment and study treatment administration is made, the PSRT (and DSMB, if applicable) will record its judgment in a memorandum to the study file held by the IND Sponsor. The IND Sponsor will instruct the clinical site to resume activities upon receipt of written notification from the PSRT. As needed, the appropriate regulatory authorities and IRBs will be informed by the IND Sponsor, in writing, of the decision to resume or discontinue study activities. The IND Sponsor is also responsible for notifying the FDA.

12.4 Corrective Actions and Reporting Events to Participants

The PSRT (in conjunction with the DSMB) will determine whether the incident constitutes an AE or UP involving risks to participants or others and may specify any corrective actions.

Corrective actions may include, but are not limited to the following:

- Acknowledgement/acceptance without further recommendation
- A request for further clarification or a corrective action plan from the IND Sponsor or study PI
- Changes in the protocol (e.g., additional tests or visits to detect similar events in a timely manner, changes to the confidentiality measures employed in the study, changes to inclusion/exclusion criteria)
- Changes to the ICFs
- Notification to enrolled participants and/or re-consenting when appropriate
- A change in frequency of continuing review
- Additional training for site PIs and/or research staff
- PSA suspension or termination

13 STATISTICAL CONSIDERATIONS

The platform trial design allows for more efficient evaluation of multiple IPs through shared controls of similarly eligible, concurrently randomized participants.

The Statistical Analysis Plan (SAP) for any IP will be finalized prior to the first planned analysis. This section is a summary of the planned statistical analyses of the primary endpoints for the early treatment and post-exposure prophylaxis indications. Each PSA will include a more detailed description of the statistical analyses outlined in this section. The PSA will also detail secondary endpoints and any additional simulations used to inform the sample size estimates.

In general, for comparative analyses (IP to control), the control group will be limited to those participants who were eligible to receive the IP being evaluated and were concurrently randomized to a relevant control arm.

13.1 Hypotheses

Early Treatment: The primary hypothesis is that early treatment with IP among low-risk outpatients infected with SARS-CoV-2 can shorten time to sustained symptom alleviation or resolution compared to standard care.

Post-exposure Prophylaxis: The primary hypothesis is that post-exposure prophylaxis with IP can prevent COVID-19 infection among close contacts of symptomatic SARS-CoV-2 positive cases compared to standard care.

13.2 Populations for Analysis

For purposes of analysis, the following analysis sets are defined:

Full Analysis Population:

All participants completing the second randomization step (randomization to a PSA)

Modified Intention to Treat (mITT) Population:

All participants randomized who receive at least one dose of the IP/control.

For the primary analysis, the mITT population will be used for the primary efficacy assessment. The mITT set will be used for all other secondary efficacy analyses

Safety Population:

All participants who receive at least one dose of the IP/control. In the unlikely case a participant receives the incorrect study drug, participants will be grouped according to the treatments that they received.

The Safety population will be used in the analyses of the safety data.

Per Protocol:

All participants in the mITT set who completed treatment with IP/control and without major protocol deviations that impact the primary efficacy evaluation. Prior to study unblinding, protocol deviations will be reviewed and a determination of the population for per protocol analysis will be made.

The PP analysis population may be used for secondary and exploratory endpoints. General Considerations

Baseline demographic and clinical variables will be summarized by treatment group using the Full Analysis population. Descriptive summaries of the distribution of continuous variables will be presented using percentiles (e.g., median, 25th and 75th percentiles), means and standard deviations. Categorical variables will be summarized using frequencies and percentages.

For binary endpoints, proportion of participants with the event will be summarized by treatment group. Comparison between groups will be presented as the difference of proportions with its 95% confidence interval. For categorical endpoints, proportion of participants in each category will be summarized by treatment group.

13.3 Primary Endpoint/Estimand Analysis

13.3.1 Early Treatment

The primary efficacy assessment is the relative time to sustained alleviation or resolution of symptomatic COVID-19 infection for a participant that receives the IP compared to a participant that does not receive the IP. Targeted symptoms will be used for analysis (Supplement 3). Sustained alleviation or resolution will be defined as the number of days from randomization within a PSA (randomization Step 2) to the first day the participant reports all symptoms as mild or none (≤ 1 or returning to pre-illness levels) for at least 3 consecutive days (the first day being considered the Event Day). The estimand of interest is the hazard ratio of a participant that has symptomatic COVID-19 with standard of care background therapy when starting treatment with IP compared to control. The primary analysis population is the mITT population.

The primary analysis model is a Cox proportional hazards model for the time to sustained alleviation or resolution of COVID-19 symptoms, with treatment arm (IP vs control) as a covariate. The model estimated hazard ratio will be used as the estimator for the estimand of interest. The estimate and 95% confidence interval for the hazard ratio will be presented.

The primary hypothesis test is that IP increases the hazard (decreases time to alleviation or resolution of COVID-19 symptoms). A hypothesis test will be conducted for testing whether the IP hazard ratio is less than 1 at a one-sided 2.5% level.

13.3.2 Post-Exposure Prophylaxis

The estimand of interest is the odds ratio of a participant that has potentially been exposed to COVID-19 suffering a symptomatic COVID-19 infection with IP compared to no control. The primary analysis population is the modified intent-to-treat population.

The primary analysis model is a logistic regression model for the likelihood of a symptomatic COVID-19 infection, with treatment arm (IP vs control) as a covariate. The model estimated odds ratio will be used as the estimator for the estimand of interest. The estimate and 95% confidence interval for the odds-ratio will be presented.

The primary hypothesis test is IP reduces the risk (odds) of symptomatic COVID-19 infections among contacts of symptomatic SARS-CoV-2 positive cases compared to placebo. A hypothesis test will be conducted for testing whether IP reduces the risk at a one-sided 2.5% level.

13.4 Outcome Measures and Statistical Analysis

Refer to PSA for detailed descriptions of outcome measures and planned statistical analysis

13.4.1 Early Treatment

13.4.1.1 Primary Outcome

- Time to sustained alleviation or resolution of COVID-19 symptoms evaluated from Day 0 through Day 28 assessed via completion of a Daily Follow Up Symptom Questionnaire.

Sustained alleviation or resolution will be defined as the number of days from randomization within a PSA to the first day the participant reports all symptoms as mild or none (≤ 1 or returning to pre-illness levels) for at least 3 consecutive days (the first day being considered the Event Day). Targeted symptoms will be used for analysis (Supplement 3).

Symptoms will be collected at Enrollment using this Screening Symptom Questionnaire. Symptom eligibility requirements for enrollment will be determined using the Symptom Questionnaire and to establish baseline symptom status. Enrollment, randomization within a PSA (randomization Step 2), and IP administration/initiation will occur on the same day.

The primary analysis is a Cox proportional hazards model with treatment assignment as a fixed covariate with a proportional effect. A one-sided p-value for the test of a hazards ratio of 1 compared to the alternative of a hazard ratio greater than 1 (IP reduces time to resolution of symptoms) will be presented and used for testing superiority.

The hazard ratio for the time to sustained alleviation or resolution of COVID-19 will be presented with 95% confidence intervals. Additional sensitivity analyses for the primary analysis will utilize additional covariate adjustments in the Cox proportional hazards model.

13.4.1.2 Key Secondary Outcomes

Key secondary outcome for the Early Treatment indication include:

- Number and proportion of all cause hospitalizations
- Number and proportion of all cause deaths

The mITT population will be used for secondary endpoint analyses

Refer to PSA

13.4.1.3 Safety and Tolerability

Refer to PSA

13.4.1.4 Exploratory

Refer to PSA

13.4.1.5 Sub-Group Analyses

Refer to PSA

13.4.2 Post Exposure Prophylaxis

13.4.2.1 Primary Outcome

- Incidence of symptomatic COVID-19 by Day 14

Symptomatic COVID-19 will be defined as a positive SARS-CoV-2 RT-PCR test and the presence of at least one COVID-19 symptom. COVID-19 symptoms will be ascertained using the Daily Follow Up Symptom Questionnaire.

The primary analysis is a logistic regression model with treatment assignment as a fixed covariate. A one-sided p-value for the test of an odds-ratio of 1 compared to the alternative of an odds-ratio less than 1 (IP reduces incidence) will be presented and used for testing superiority.

The odds ratio for the incidence of symptomatic COVID-19 will be presented with 95% confidence intervals. Additional sensitivity analyses for the primary analysis will utilize additional covariate adjustments in the logistic regression model.

13.4.2.2 Secondary Outcomes

Refer to PSA

13.4.2.3 Safety and Tolerability

Refer to PSA

13.4.2.4 Exploratory

Refer to PSA

13.4.2.5 Sub-Group Analyses

Refer to PSA

13.5 Interim Analysis Plan

The adaptive elements, including the interim analysis schedule and plan will be detailed in each PSA.

13.6 Final Analysis Plan

The adaptive elements, including the interim analysis schedule and plan will be detailed in each PSA.

13.7 Missing Data

The primary analyses for each population will be based on an intent-to-treat approach. Therefore, every patient in the intent-to-treat group will be analyzed. A single imputation approach for each patient with missing data will be utilized with a range of sensitivity analyses exploring the sensitivity of the results to the missing data.

For the Early Treatment population, the primary analysis is a time to sustained alleviation or resolution of symptoms analysis. For a patient that becomes lost-to-follow-up and hence is missing the full primary outcome, a last-status imputation will be assumed. If the patient's last day was symptom free, then the patient will be assumed symptom free, and their time of resolution will be the first symptom free day. If the patient's last day was symptoms alleviated, then the patient will be assumed symptom alleviated and their time of alleviation the first day of alleviated symptoms. If the patient's last day was non-alleviated or resolved symptoms, they will be assumed censored without alleviation or resolution at the last observed day.

For the PEP population, a single imputation approach will be conducted for the primary analysis for each patient with missing daily observations. The following single imputation will be utilized:

- A patient that tests negative and has missing daily outcomes will have their negative status carried forward and be considered negative for the primary analysis.
- If a participant tests positive for COVID-19 and has missing symptom scores through Day 14 will be considered a positive symptomatic case.

The details of the missing data imputations and the sensitivity analyses will be detailed in the individual appendices Statistical Analysis Plans.

13.8 Sample Size Determination

13.8.1 Early Treatment

The maximum sample size for the early treatment indication primary analysis is 300 participants with 1:1 allocation to the IP and its control arm. The maximum sample size of 300 participants (150 active and 150 controls) and the adaptive design provides 90% power to detect a hazard ratio of 1.50 risk (33% reduction in median time to symptom alleviation or resolution) and approximately 80% power for a hazard ratio of 1.42, a 30% reduction in the median time to symptom alleviation or resolution, assuming a median time to symptom resolution of 9 days for the control arm. This assumption is based on review of relevant literature [Menni 2022, Akavian 2022].

13.8.2 Post-Exposure Prophylaxis

The maximum sample size for the primary analysis is 700 participants with 1:1 allocation to the IP arm and its control arm. The maximum sample size of 700 participants (350 active and 350 controls) provides 95% power to detect a reduction in the odds of a symptomatic COVID-19 infection assuming a control participant is at a 20% risk of symptomatic infection and the IP reduces the risk of infection by 50%. The sample size provides approximately 80% power to detect a 40% reduction in the risk of symptomatic infection.

14 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

14.1 Regulatory, Ethical, and Study Oversight Considerations

14.1.1 Regulatory Review

The United States Food and Drug Administration (FDA), Central IRB (Advarra), US Department of Defense Human Subjects Protection Office – USAMRMC HRPO, clinical trial site IRBs, and relevant local health authorities will be asked to review and give written approval of the protocol and the informed consent forms, and all other written information provided to the participant.

14.1.2 Informed Consent Process and Informational Documents Provided to Participants

Similar to the study randomization process, the informed consent process will occur in 2 steps.

The initial step will be the screening informed consent. This will consist of an overview of the study master protocol, study objectives, the randomization process, and the study duration. The eligibility criteria and screening procedures will be covered in detail in the Screening ICF. This information will be provided to the participant and written documentation of informed consent will be required prior to starting any screening procedures.

The second step will be the PSA Informed Consent. Participants meeting the eligibility criteria after completion of the screening process will be randomized to an appropriate PSA for which they are eligible and receive the PSA ICF. The PSA ICF will be specific to the IP and will describe in detail the study intervention, the second step of the randomization process, blinding, study procedures, and potential benefits and risks. This information will be provided to the participant and written documentation of informed consent will be required prior to starting intervention/administering study intervention.

If eligible to contribute to a shared placebo pool (i.e., participant potentially meets eligibility criteria for more than one PSA participating in placebo sharing), the participant will complete informed consent for all PSA ICFs for which they may be eligible and that are contributing to a shared placebo pool.

14.1.3 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The study will use a two-step informed consent process. The first will be the screening informed consent and the second will be a product-specific informed consent. Due to the contagious nature of the emergent infectious diseases being studied under this protocol and understanding recruitment of contacts may not always take place in person, it may not always be feasible for study staff to come in direct contact with the potential and/or active study participants or handle any items that they may have come in contact with per local site infection control policies. Therefore, obtaining signed Informed Consent Forms (ICF) and authorization for use and disclosure of protected health information (if applicable) for participants enrolled in this study may not always be feasible for study staff. In these instances, for the **screening informed consent only**, the study team may request a waiver of documentation of signed screening informed consent. When possible, the participant will provide signed screening ICF. If the participant is unable to provide signed screening consent, the waiver of documentation of signed screening informed consent will be utilized, allowing the participant to provide verbal, rather than written screening consent. If study personnel are unable to work near the potential and/or active participant for safety reasons, the study personnel will contact the participant according to the requirements of the site. Options may include but are not limited to speaking with the participant from a safe distance in person, contacting the patient by phone, in person with a barrier in between the potential and/or active participant and the study personnel, contacting the patient by phone from a separate location, video conferencing, or having a study physician trained in infectious disease safety procedures meet with the potential and/or active participant in close proximity (if allowed by the site). An observer (witness) will be present for all verbal screening consents. The observer's name and signature documenting the review of the verbal screening consent will be documented on the Screening Consent Form Checklist. The observer may be an individual on the site study staff who is not part of the participant's screening consent process.

In contrast to the screening informed consent, the **product-specific informed consent will require** the consent process to take place in person with a signed ICF and authorization for use and disclosure of protected health information (if applicable). Consent will be performed in as private a manner as possible. The potential and/or active participant will be thoroughly briefed on the study's Informed Consent and authorization for use and disclosure of protected health information. They will also be provided with an opportunity to ask any questions and an unsigned copy of the informed consent if permissible by the site. In turn, study staff will thoroughly document the informed consent process in the study chart. The study personnel designated to conduct consent will sign and file the ICF.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be offered to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

For site locations enrolling non-English speaking participants, the consent documents (and other participant facing documents) will be translated into the relevant language to ensure proper

participant understanding. A study staff member who speaks the relevant language and is designated to will conduct the informed consent using the appropriate translated documents.

For participants enrolled who are illiterate and cannot read the consent form, an impartial witness must be present during the consenting process (for both English and non-English speaking participants). The impartial witness' name and signature documenting the review of the consent will be documented on the consent reviewed (either Screening ICF or product specific ICF). The impartial witness may be an individual on the site study staff who is not part of the participant's consent process.

14.1.4 Study Discontinuation and Closure

This study or PSA may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Determination of study or PSA suspension or termination may be made by the IND Sponsor, the Study PI, PSRT or DSMB. PSA suspension or termination may be made by Industry Supporter. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to study participants, investigators, Study funder, IND Sponsor, industry supporters, and regulatory authorities. If the study or PSA is prematurely terminated or suspended, the IND Sponsor will promptly inform study participants, Study PI, site PIs, the IRB and industry supporters and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant early declaration (Section 5.1.3 Early Termination)
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility (Section 5.1.3 Early Termination)

14.1.5 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the IND sponsor(s), the study funder, and the industry supporter(s). This confidentiality is extended to cover testing of biological specimens in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the industry supporter(s).

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the IND sponsor, representatives of the IRBs, regulatory agencies, the study funder, or the industry supporter supplying study product

may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated in clinical trial agreement as prescribed by the reviewing IRB, Institutional policies, the study funder, the IND sponsor, local regulatory authorities, the US Food and Drug Administration or industry supporter(s) requirements.

Study participant research electronic data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within IND Sponsor's secure, HIPAA compliant electronic data capture systems and clinical data repository using the Clinical One application, a 21 CFR Part 11-compliant data capture system provided by IND Sponsor. This data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical trial sites and by IND Sponsor research staff will be secured, and password protected.

14.1.6 Future Use of Stored Specimens and Data

With the participant's approval, and as approved by local IRBs, de-identified biological specimens will be stored at the study implementer site, Henry M. Jackson Foundation for the Advancement of Military Medicine Inc. (HJF), and at associated partners' sites with the same goal as the sharing of data with HJF. These specimens could be used for research to understand the natural history of COVID-19 including its clinical course, disease biology and pathology and will be shared with clinical trial site member upon request under an appropriate agreement such as a Materials Transfer Agreement (MTA). Protocols that will utilize specimens and data collected from this study for future use will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent regarding biospecimen storage may not be possible after the study is completed.

When product-specific endpoints are completed and the results unblinded, access to study data and/or specimens will be provided through HJF which will derive data from the HJF-managed, HIPAA-compliant, specimen and data management system.

14.1.7 Key Roles and Study Governance

Key Role	**Name**	**Institution**
Principal Investigator	Kristen Pettrone	HJF
CRO Project Manager	Nancy Cameron	FHI Clinical

14.1.8 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including experts in the clinical aspects of COVID-19, biostatisticians, investigators (not directly involved in his study) with expertise in current clinical trials conduct and methodology. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the IND sponsor and the core investigative team at HJF.

14.1.9 Clinical Monitoring

Clinical trial site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by IND Sponsor in conjunction with the medical monitor.

- Details of clinical trial site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- HJF and/or IND Sponsor will conduct site initiation visits (in person or remote) at each site before the study begins enrollment.
- Clinical monitoring will be a combination of on-site and remote monitoring.

14.1.10 Quality Assurance and Quality Control

Each clinical trial site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices [GMP]).

The clinical trial site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the IND Sponsor, and inspection by local and regulatory authorities

14.1.11 Data Handling and Record Keeping

The principal investigator and delegated research personnel will manage all study data, including paper and electronic files.

Study documents will be stored at each facility in a locked space or file with access limited to study personnel. Participant identities will be protected by a unique study I.D. number and linking identification (i.e., the informed consent document and enrollment log) will be kept separately from test results, in locked files, with limited access. Electronic data will be handled in a confidential, controlled-access fashion in accordance with HJF's "Use Restricted" classification of data security and privacy policies (Policy Number: HJF-0501, "Information Classification and Data Protection Policy", Revision Effective Date: 2019-10-24). The study enrollment log will contain a unique study ID (specific to the participant), their name, phone numbers, email address, and mailing address.

The informed consent documents will contain the same unique study ID number and the participant's name. The case report form may include the participant's unique identifier number, sex, age, email address, ethnicity, medical history, vaccinations history, living and working conditions, and behaviors.

The participant will have the right to revoke the authorization for use of his/her Protected Health Information (PHI) and this will be made clear, along with procedures for doing so, in the informed consent and assent documents.

14.1.12 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the clinical database derived from source documents should be consistent with the data recorded on the source documents. Sites may use either paper CRF or direct data entry into the clinical database for their method of data collection. The site must document which CRF, if any, will be used as source documents in an SOP for source documentation.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the Clinical One application. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. All data transmitted to and from the application is done using a secure, encrypted transmission (SSL/HTTPS). Clinical One has an audit trail function in which all changes are tracked and attributable to individual users. Case report forms will be

checked for completeness and consistency in accordance with the Data Management Plan and source document verified as part of study monitoring.

14.1.13 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the IND Sponsor, if applicable. It is the responsibility of the IND Sponsor to inform the investigator when these documents no longer need to be retained. Informed Consent forms will be stored in accordance with HIPAA Regulations.

14.1.14 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Study Specific Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the clinical trial site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the IND Sponsor, the HJF Clinical Research Associate, and the HJF Data Manager. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

14.1.15 Publication and Data Sharing Policy

Sharing of the data generated by this study is considered a moral obligation for improved knowledge (including negative outcomes) of an unregistered product considered potentially lifesaving in COVID-19 disease. Published data will adhere to the principles as outlined in the World Health Organization’s 2020 Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D [WHO reference number: WHO/RFH/20.1].

As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

MTAs for data and clinical specimen sharing will be established with all collaborating partners in the U.S. and internationally.

14.1.16 Conflict of Interest Policy

The independence of this clinical trial from any actual or perceived influence, such as by the biopharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with IND Sponsor and HJF has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

15 ADDITIONAL CONSIDERATIONS

Refer to PSAs if applicable.

This section should include a description of any additional considerations not currently covered in this protocol template, such as particular institutional or IRB-related requirements.

16 ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transferase
AST	Aspartate Aminotransferase
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
DAIDS	Division of AIDS
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FHIC	FHI Clinical
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HJF	Henry M. Jackson Foundation for the Advancement of Military Medicine Inc.
HRPO	Human Research Protections Office
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IxRS	Interactive Voice/Web Response System
JPEO	Joint Program Executive Office
mITT	Modified Intention to Treat
MOP	Manual of Procedures

MTA	Materials Transfer Agreement
NP	Nasopharyngeal
PEP	Post-Exposure Prophylaxis
PHI	Protected Health Information
PI	Principal Investigator
POC	Point of Care
PSA	Product Specific Appendix
PSRT	Protocol Safety Review Team
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
QC	Quality Control
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reactions
TEAE	Treatment Emergent Adverse Events
UP	Unanticipated Problem
US	United States
VOC	Variant of Concern
VOI	Variant of Interest
WHO	World Health Organization

17 STUDY-SPECIFIC DEFINITIONS

Arms within PSA	Once randomized to a specific IP (PSA), second randomization to arms within the PSA. The default is two arms: investigational product and control. Arms within the PSA will be detailed in the product specific appendix.
Hospitalization	Admission to an acute care facility for longer than 24 hours where medical care is delivered to treat and stabilize an emergent condition. Hospitalization does not include admission for isolation or quarantine purposes or for social admissions such as breakdown of home support
Indication	Indication is the valid reason to use the investigational product. For this protocol the indication refers to either early treatment of COVID-19 or post-exposure prophylaxis
Product Specific Appendix (PSA)	Appendix to the master protocol detailing product specific information. Also refers to the product-specific arm of the study a participant is randomized to after completion of the screening and enrollment process and all the study procedures contained within it.
Strata	Categorization of therapeutic indications within the trial: Early Treatment or Post-Exposure Prophylaxis
Stratification	From the results of the screening process, categorization of participants as: 1) Symptomatic SARS-CoV-2 positive cases OR 2) Asymptomatic contacts of symptomatic SARS-CoV-2 positive cases

18 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
V 1.0	18 Mar 2022	NA	Initial Protocol
V 2.0	26 April 2023	Updated formatting and sections.	Consistency.
	26 April 2023	Updated section and figure numbering.	Consistency.
	26 April 2023	Added boxes for Site Investigator Name, Title, Signature, and Date	Improve formatting.
	26 April 2023	Updated study design to clarify that the study is low risk, Phase 2, and each PSA will provide details for the investigational products (IP).	Clarified for clear expectations.
	26 April 2023	Removed Week 24 visit.	Shorten study follow-up period.
	26 April 2023	Updated Study Population A.	Simplify the population definition.
	26 April 2023	Updated Outcome Measures with the primary efficacy assessment for both the early treatment and post-exposure prophylaxis indications.	Clarified for clear expectations.
	26 April 2023	Updated study visits to clarify activities and procedures.	Clarified for clear expectations.
	26 April 2023	Added reference information.	Correct formatting.
	26 April 2023	Added additional references to include most up to date information on SARS-CoV-2 since previous version.	New information.
	26 April 2023	Added Early Treatment and Post-exposure Prophylaxis hypotheses.	Include study hypothesis for the Master protocol.
	26 April 2023	Added objectives and endpoints for the Early Treatment and Post-Exposure Prophylaxis indications.	Include objectives and endpoints for the Master protocol.

Version	Date	Description of Change	Brief Rationale
	26 April 2023	Added selection criteria for IP and clarified that two physicians will evaluate the criteria in order to determine IP eligibility.	Clarify selection process.
	26 April 2023	Population A updated to add list of Screening Symptoms to Supplement 3 and explain the symptom rating for preexisting conditions. Population B updated to clarify that contacts must have indoor exposure to the symptomatic case.	Updated the list of SARS-CoV-2 symptoms and exposure definition to be in line with current guidance.
	26 April 2023	Population A updated to include oxygen saturation or use of supplemental oxygen at enrollment and added a list of comorbidities. Added information about women of childbearing potential for both Population A and B.	Clarified for clear expectations.
	26 April 2023	Added that participants are asked not to participate in another clinical trial with an IP during their enrollment in this trial.	Clarified for clear expectations.
	26 April 2023	Added new section.	Consistency.
	26 April 2023	Added that adherence reminders will take place with the Daily Follow Up Symptom Questionnaire and study staff will review dosing instructions.	Updated to improve patient adherence.
	26 April 2023	Updated the definition of concomitant therapy and listed specific exceptions that do not need to be recorded.	Clarified for clear expectations.
	26 April 2023	Added *Figure 4. Second Randomization Step: IPs with SOC treatment allocation.*	Provide a figure for clarification.
	26 April 2023	Updated language to clarify the differences between participant discontinuation of IP, withdrawal of consent, and lost to follow-up.	Clarified for clear expectations.

Version	Date	Description of Change	Brief Rationale
	26 April 2023	Updated the key efficacy assessment for the early treatment indication as time to sustained alleviation or resolution of targeted symptoms as determined by subject responses on the Daily Follow Up Symptom Questionnaire.	Clarify how efficacy assessments will be determined.
	26 April 2023	Added details about the Screening Symptoms Questionnaire and Daily Follow Up Symptom Questionnaire and how these will be completed by subjects.	Clarify how symptoms will be reviewed.
	26 April 2023	Updated the SARS-CoV-2 Testing section to add that a core laboratory will be used for all study testing and identified which assays and platforms will be used.	Added additional testing details.
	26 April 2023	Added new section to clarify PSAs will detail the screening assessment requirements and final eligibility will be determined by site PIs after review.	Consistency.
	26 April 2023	Added new section.	Consistency.
	26 April 2023	Added new section to provide definition for a treatment emergent adverse event.	Consistency.
	26 April 2023	Added new section to define SUSAR and outline reporting requirements to Sponsor and FDA.	Added per FDA recommendation.
	26 April 2023	Added new section to outline how AE and SAE data will be identified by study staff throughout the study.	Added per FDA recommendation.
	26 April 2023	Added new section to provide guidance on SAE follow-up.	Added per FDA recommendation.
	26 April 2023	Added information about a medical monitor and their responsibilities throughout the study.	Added per FDA recommendation.

Version	Date	Description of Change	Brief Rationale
	26 April 2023	Updated details about DSMB meeting frequency and responsibilities.	Clarified for clear expectations.
	26 April 2023	Added and updated sections to outline pause and stopping criteria at the individual participant or Study/PSA level.	Added per FDA recommendation.
	26 April 2023	Added details about the Statistical Analysis Plan (SAP) to include the primary hypotheses, primary endpoint/estimand analysis, outcome measures and statistical analysis, and sample size determination for the early treatment and post-exposure prophylaxis indications	Update the SAP with additional information.
	26 April 2023	Updated CRO Project Manager	Personnel change
	26 April 2023	Added new questionnaires to record participant symptoms at screening and then during follow up.	Updated to support study hypotheses.
	26 April 2023	Added list of COVID-19 symptoms to be used for Screening, Daily Follow Up, and Analysis.	Updated to most current list of symptoms.
V 3.0	02 June 2023	Updated exclusion criteria related to contraceptive use to specify time period for use.	Clarified for clear expectations.
V4.0	01 November 2023	Removed contraceptive requirement for women of childbearing potential	Moved to PSA as will be product specific. Changed from exclusion to inclusion criteria in the PSA
	01 November 2023	Updated SUSAR definition to be consistent with current standards of “serious” and “unexpected”	Clarification

Version	Date	Description of Change	Brief Rationale
	01 November 2023	Added description of symptom severity: None- You did not experience the symptom at all, Mild- You experienced the symptom, but it did not affect your ability to function, Moderate- You experienced the symptom, and it reduced your ability to function, Severe- You experienced the symptom, and it greatly limited your ability to function.	Added detail to assist participants with completion of symptom questionnaires
	01 November 2023	Updated treatment guidelines and data to support study rationale	Updated data
	01 November 2023	Clarified testing window for HIV CD4 count and Viral load (30 days from enrollment) and reported compliance with ART (if applicable)	Clarification of eligibility criteria
	01 November 2023	Clarified relatedness to IP or study procedure	DSMB feedback
	01 November 2023	Changed bullets to numbering	Data monitoring request
	01 November 2023	Added requirement to record nicotine replacement therapy and herbal supplements	FDA recommendation
	01 November 2023	Increased BMI restriction from 25 to 30 kg/m^2	Expand eligibility criteria
	01 November 2023	Clarified mITT population will be used for secondary endpoint analyses	FDA request
	01 November 2023	Updated personnel: Removed Dr. Blair Updated PM for CRO (FHI)	Updated study roles

Version	Date	Description of Change	Brief Rationale
V5.0	07 February 2024	Clarified the ability for PSAs to choose to participate or not participate in placebo sharing Clarified participants must meet final eligibility criteria for all PSAs for which they are eligible and contributing to a shared placebo pool	Clarification on placebo sharing for PSAs and participants
	07 February 2024	Clarified the ability for PSAs to choose to participate or not participate in placebo sharing Clarified participants must meet final eligibility criteria for all PSAs for which they are eligible and contributing to a shared placebo pool	Clarification on placebo sharing
	07 February 2024	Updated figure to clarify flow for participant eligibility for multiple PSAs contributing to shared placebo pool	Clarification on placebo sharing
	07 February 2024	Clarified that participants must complete PSA informed consent for all PSAs for which they may be eligible and are contributing to a shared placebo pool	Clarification on participant eligibility assessment for placebo sharing
	07 February 2024	Clarified order of activities to reflect Informed Consent and MP/PSA screening assessments	Clarification on order to activities for participants to complete PSA ICF and eligibility assessments prior to Step 1 randomization
	07 February 2024	Expanded study population to include standard and intermediate risk participants (revised high risk exclusion criteria per FDA Type D Meeting Request Written Response)	FDA feedback to Type D Meeting Request
	07 February 2024	Clarified screening assessments under Master Protocol	Clarification of requirements for screening under Master Protocol

Version	Date	Description of Change	Brief Rationale
	07 February 2024	Added rationale for expansion of the study population to standard and intermediate risk	Rational to support study population expansion

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20 SUPPLEMENT 1: SCREENING SYMPTOM QUESTIONNAIRE

Screening Symptom Questionnaire Source Document **SSQ**

PROTECT-APT 1 **Early Treatment and Post-Exposure Prophylaxis of COVID-19 - Adaptive Platform Trial**

Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐ **Visit Date** ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

☐ Not Done

Symptom Questions

For items 1-11, what was the severity of each symptom below at its worst over the last 24 hours?	**None** (You did not experience the symptom at all)	**Mild** (You experienced the symptom, but it did not affect your ability to function)	**Moderate** (You experienced the symptom, and it reduced your ability to function)	**Severe** (You experienced the symptom at a level which greatly limited your ability to function)
1. Stuffy or runny nose	☐	☐	☐	☐
1a. Do you usually have a stuffy or runny nose? ☐ Yes ☐ No				
1b. What is the usual severity?	☐	☐	☐	☐
2. Sore throat (painful, scratchy, or irritated)	☐	☐	☐	☐
2a. Do you usually have a sore throat? ☐ Yes ☐ No				
2b. What is the usual severity?	☐	☐	☐	☐

Screening Symptom Questionnaire Source Document **SSQ**

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Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐ **Visit Date** ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

3. Hoarse voice (raspy, strained, or abnormal voice)	☐	☐	☐	☐
3a. Do you usually have a hoarse voice? ☐ Yes ☐ No				
3b. What is the usual severity?	☐	☐	☐	☐
4. Shortness of breath (difficulty breathing)	☐	☐	☐	☐
4a. Do you usually have shortness of breath ☐ Yes ☐ No				
4b. What is the usual severity?	☐	☐	☐	☐
5. Cough	☐	☐	☐	☐
5a. Do you usually have a cough? ☐ Yes ☐ No				
5b. What is the usual severity?	☐	☐	☐	☐
6. Low energy or tiredness	☐	☐	☐	☐
6a. Do you usually have low energy or tiredness? ☐ Yes ☐ No				
6b. What is the usual severity?	☐	☐	☐	☐

Screening Symptom Questionnaire Source Document **SSQ**

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Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐ **Visit Date** ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

7. Muscle or body aches	☐	☐	☐	☐
7a. Do you usually have muscle or body aches? ☐ Yes ☐ No				
7b. What is the usual severity?	☐	☐	☐	☐
	None	Mild	Moderate	Severe
8. Headache	☐	☐	☐	☐
8a. Do you usually have a headache? ☐ Yes ☐ No				
8b. What is the usual severity?	☐	☐	☐	☐
9. Chills or shivering (feeling of coldness or shaking when not in a cold environment)	☐	☐	☐	☐
9a. Do you usually have chills or shivering? ☐ Yes ☐ No				
9b. What is the usual severity?	☐	☐	☐	☐
10. Feeling hot or feverish	☐	☐	☐	☐
10a. Do you usually feel hot or feverish? ☐ Yes ☐ No				
10b. What is the usual severity?	☐	☐	☐	☐

Screening Symptom Questionnaire Source Document **SSQ**

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Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐ **Visit Date** ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

11. Nausea (feeling like you wanted to throw up)	☐	☐	☐	☐
11a. Do you usually have nausea? ☐ Yes ☐ No				
11b. What is the usual severity?	☐	☐	☐	☐
12. How many times did you vomit (throw up) in the last 24 hours?	☐ I did not vomit at all ☐ 1 or 2 times ☐ 3 or 4 times ☐ 5 or more times			
13. How many times did you have diarrhea (loose or watery or more frequent bowel movements) in the last 24 hours?	☐ I did not have diarrhea at all ☐ 1 or 2 times ☐ 3 or 4 times ☐ 5 or more times			
14. Rate your sense of smell in the last 24 hours:	☐ My sense of smell is THE SAME AS usual ☐ My sense of smell is LESS THAN usual ☐ I have NO sense of smell			
15. Rate your sense of taste in the last 24 hours:	☐ My sense of taste is THE SAME AS usual ☐ My sense of taste is LESS THAN usual ☐ I have NO sense of taste			

Screening Symptom Questionnaire Source Document **SSQ**

PROTECT-APT 1 **Early Treatment and Post-Exposure Prophylaxis of COVID-19 - Adaptive Platform Trial**

Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐ **Visit Date** ☐☐ ☐☐ ☐☐☐☐

(MM/DD/YYYY)

Overall Symptom Severity

16. In the past 24 hours, what was the severity of your overall COVID-19 related symptoms at their worst?	None	Mild	Moderate	Severe
	☐	☐	☐	☐

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20.1 Supplement 2: Daily Follow Up Symptom Questionnaire

Daily Follow Up Symptom Self Report Questionnaire Source Document **DSQ**

PROTECT-APT 1 **Early Treatment and Post-Exposure Prophylaxis of COVID-19 - Adaptive Platform Trial**

Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐

Visit Date ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

☐ Not Done

Symptom Questions

For items 1-11, what was the severity of each symptom below at its worst over the last 24 hours?	**None** (You did not experience the symptom at all)	**Mild** (You experienced the symptom, but it did not affect your ability to function)	**Moderate** (You experienced the symptom, and it reduced your ability to function)	**Severe** (You experienced the symptom at a level which greatly limited your ability to function)
1. Stuffy or runny nose	☐	☐	☐	☐
2. Sore throat (painful, scratchy, or irritated)	☐	☐	☐	☐
3. Hoarse voice (raspy, strained, or abnormal voice)	☐	☐	☐	☐
4. Shortness of breath (difficulty breathing)	☐	☐	☐	☐
5. Cough	☐	☐	☐	☐

Daily Follow Up Symptom Self Report Questionnaire Source Document **DSQ**

PROTECT-APT 1 **Early Treatment and Post-Exposure Prophylaxis of COVID-19 - Adaptive Platform Trial**

Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐

Visit Date ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

6. Low energy or tiredness	☐	☐	☐	☐
7. Muscle or body aches	☐	☐	☐	☐
8. Headache	☐	☐	☐	☐
9. Chills or shivering (feeling of coldness or shaking when not in a cold environment)	☐	☐	☐	☐
10. Feeling hot or feverish	☐	☐	☐	☐
11. Nausea (feeling like you wanted to throw up)	☐	☐	☐	☐
12. How many times did you vomit (throw up) in the last 24 hours?	☐ I did not vomit at all ☐ 1 or 2 times		☐ 3 or 4 times ☐ 5 or more times	
13. How many times did you have diarrhea (loose or watery or more frequent bowel movements) in the last 24 hours?	☐ I did not have diarrhea at all ☐ 1 or 2 times		☐ 3 or 4 times ☐ 5 or more times	
14. Rate your sense of smell in the last 24 hours:	☐ My sense of smell is THE SAME AS usual ☐ My sense of smell is LESS THAN usual ☐ I have NO sense of smell			

Daily Follow Up Symptom Self Report Questionnaire Source Document **DSQ**

PROTECT-APT 1 **Early Treatment and Post-Exposure Prophylaxis of COVID-19 - Adaptive Platform Trial**

Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐ **Visit Date** ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

15. Rate your sense of taste in the last 24 hours:	☐ My sense of taste is THE SAME AS usual ☐ My sense of taste is LESS THAN usual ☐ I have NO sense of taste

Overall Symptom Severity

16. In the past 24 hours, what was the severity of your overall COVID-19 related symptoms at their worst?	None	Mild	Moderate	Severe
	☐	☐	☐	☐

Global Impression Items

17. In the past 24 hours, have you returned to your usual health (before your COVID-19 illness)?	☐ Yes ☐ No
18. In the past 24 hours, have you returned to your usual activities (before your COVID-19 illness)?	☐ Yes ☐ No
19. In the past 24 hours, have you experienced any new symptoms that are NOT listed in this questionnaire (or that you have not reported before today)?	☐ Yes ☐ No
If YES, please list all new symptoms NOT listed on this questionnaire:	_____

Daily Follow Up Symptom Self Report Questionnaire Source Document **DSQ**

PROTECT-APT 1 **Early Treatment and Post-Exposure Prophylaxis of COVID-19 - Adaptive Platform Trial**

Subject ID ☐☐☐☐ ☐☐☐☐ ☐☐☐☐☐☐☐☐ **Visit Date** ☐☐ ☐☐ ☐☐☐☐ **(MM/DD/YYYY)**

General Questions

20. Have you taken your study medication today?	☐ Yes ☐ No

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20.2 Supplement 3: COVID-19 Symptom Review

Daily Sign and Symptom Collection	Screening Symptoms	Daily Follow Up Symptoms	Targeted Symptoms for Analysis
Stuffy or runny nose	X	X	X
Hoarse voice	X	X	X
Sore throat	X	X	X
Difficulty breathing	X	X	X
Cough	X	X	X
Fatigue (Low energy or tiredness)	X	X	X
Muscle or body aches	X	X	X
Headache	X	X	X
Fever (documented temperature >38 °C [100.4 °F]) or subjective fever	X		
Chills or shivering	X	X	X
Feeling hot or feverish		X	X
Nausea	X	X	X
Vomiting	X	X	X
Diarrhea	X	X	X
Loss of Smell	X	X	X
Loss of taste	X	X	X
New symptoms in the last 24 hours		X	