CONFIDENTIAL

Selective Trial Of Paxlovid for PASC (STOP-PASC)

Randomized Double-Blind Placebo-Controlled Pilot Trial of Paxlovid for the Treatment of PASC

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IND Number:	163308
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Study Phase:	2
Study intervention:	nirmatrelvir-ritonavir (Paxlovid)
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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the 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).

All individuals who are responsible for the conduct, management, or oversight of this study 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 must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form 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.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Brief Title	Selective Trial of Paxlovid for PASC (STOP-PASC)
Study Rationale	Long COVID or post-acute sequelae of SARS-CoV-2 (PASC) encompasses a variety of symptoms that persist beyond the acute phase of COVID-19 infection and can lead to chronic debilitation. There are currently no known effective therapies for PASC and the underlying mechanisms of pathogenesis are unclear, but viral persistence is one of several leading hypotheses. Thus, the overall goal of this study is to investigate the efficacy and safety of ritonavir-boosted SARS-CoV-2 antiviral medication nirmatrelvir in participants with PASC and explore biological and digital wearable biometric markers of disease and disease severity.
Study Description	This study is an interventional efficacy and safety, phase II, double-blind, 2-arm pilot study to investigate orally administered nirmatrelvir-ritonavir (PAXLOVID™) compared with placebo-ritonavir ("placebo") in outpatient adult participants with PASC. Eligible participants will be randomized 2:1 to receive nirmatrelvir-ritonavir or placebo-ritonavir q12h for 15 days. Randomization will be stratified by vaccination status and number of core symptoms. We hypothesize that adult participants with PASC treated with Paxlovid for 15 days

	will report reduced PASC symptom(s) severity at 10 weeks compared to placebo.
Study Phase	II
Primary Objective	• To compare the efficacy of a 15-day course of Paxlovid versus placebo in reducing symptom(s) severity of participants with PASC
Secondary Objectives	• To compare overall symptom burden of participants with PASC treated with Paxlovid versus placebo • To evaluate other patient-reported outcomes (e.g., functional status, global health status, etc.) in participants with PASC treated with Paxlovid versus placebo • To identify which core PASC symptom(s) are most responsive to Paxlovid treatment, if any
Exploratory Objectives	• To investigate potential biological biomarkers of PASC in participants treated with Paxlovid versus placebo • To investigate potential digital biometric biomarkers of PASC in participants treated with Paxlovid versus placebo
Primary Endpoint	• Core symptoms severity based on Likert-scale score at 10 weeks in participants treated with Paxlovid versus placebo. Core symptoms defined as: fatigue, brain fog, dyspnea, body aches, gastrointestinal symptoms, cardiovascular symptoms
Secondary Endpoints	• Core symptoms severity based on Likert-scale score at 15 days in participants treated with Paxlovid versus placebo • Proportion of participants reporting relief at 10 weeks of at least one core symptom for 2 weeks. Relief defined as reduction of severity from moderate to none or severe to mild/none, $\geq$ 2-point Likert score change • Proportion of participants with overall alleviation at 10 weeks in Paxlovid versus placebo group for 2 weeks. Overall alleviation defined as both: (1) any core symptom(s) that are none/mild (Likert 0 or 1) at baseline are none at 10 weeks *and* (2) any core symptom(s) that are moderate/severe (Likert 2 or 3) at baseline are none/mild at 10 weeks • Severity of the most bothersome symptom at 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group • Time to relief of each of the 6 core symptoms. Relief defined as above. • Change in PROMIS Physical Function SF 4a v2.0 from baseline to 10 weeks • Change in PROMIS Fatigue SF 7a v1.0 score between baseline and 10 weeks

	• Change in PROMIS Dyspnea-Severity SF 5a v1.0 score between baseline and 10 weeks • Change in PROMIS Cognitive Function Abilities score between baseline and 10 weeks • Change in orthostatic vitals (difference in seated versus standing blood pressure and heart rate) from baseline and 10 weeks • Change in 1-minute sit-to-stand test from baseline and 10 weeks • Patient Global Impression of Severity scale (PGIS) at 15 days, 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group • Patient Global Impression of Change scale (PGIC) at Day 15, 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group
Exploratory Endpoints	• Clinical laboratory test: d-dimer • Stool RNA RT-qPCR to assess for presence of SARS-CoV-2 at baseline, 7 days, 15 days (immediately after treatment), 10 weeks (1) • Difference in drug versus placebo and change from baseline of: o O-link cytokine profiles, specific chemokines such as CCL11, others (2) o Autoantibodies – bead-based, multiplexed assays (3, 4) o Bulk RNA-Sequencing (5) o Anti-SARS-CoV-2, EBV, CMV and other IgG responses, measured in a combined panel of autoantibodies described above (3) o Proportions of blood cells measured by flow cytometry, including anti-SARS-CoV-2 T cell responses measured using spheromers (6) • Other assays that may emerge regarding PASC pathophysiology • Change in digital biometric wearables measures from baseline to 15 days, 5 weeks, 10 weeks, and 15 weeks in drug versus placebo groups for: o Physical activity (PA) measured by hand accelerometer o Ratio of daytime versus nighttime PA level o Time asleep and time in bed o Heart rate and resting heart rate o Heart rate variability o ECG rhythm abnormalities o O2 saturation o Blood pressure
Safety Monitoring	Frequency of adverse events and serious events will be analyzed in all study participants

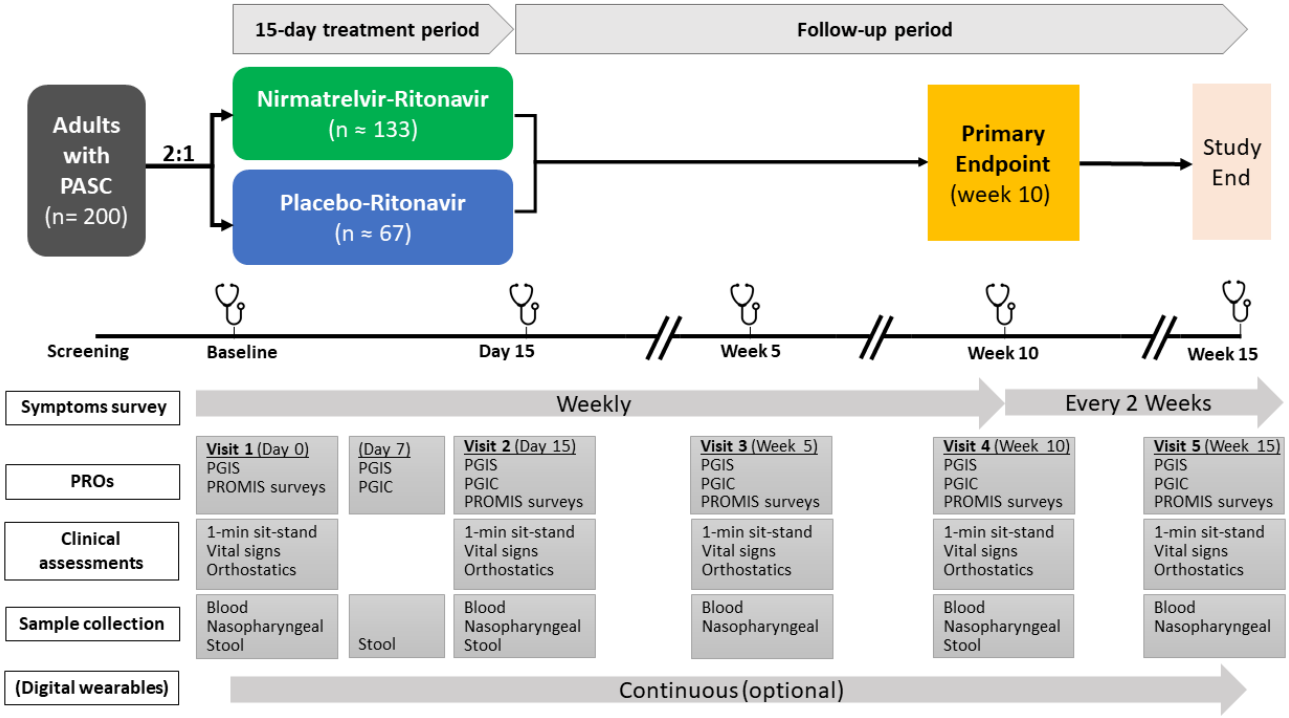
Independent Oversight Committee	An independent Data and Safety Monitoring Board (DSMB) comprised of members with relevant expertise in areas such as PASC, clinical trials, statistics, and/or virology will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the intervention during the trial, and for monitoring the overall conduct of the clinical trial. The DSMB will provide recommendations about stopping or continuing the trial or other protocol recommendations as deemed appropriate to enhance the integrity of the trial.
Study Population	200 adults with PASC will be randomized
Study Location	Single site – Stanford University
Study Intervention	• Nirmatrelvir (PF- 07321332) 300 mg (two 150mg tablets) plus ritonavir 100mg orally q12h for 15 days, OR • Matched placebo for nirmatrelvir (two tablets) plus ritonavir 100mg orally q12h for 15 days
Study Duration	Entire study is estimated to last up to 12 months from first participant enrolled until the end-of-study for the last participant enrolled
Participant Duration	For each participant, the study lasts 15 weeks (3.5 months)
Inclusion Criteria	1. Adults 18 years and older 2. Weight > 40 Kg 3. Normal or near-normal renal function (eGFR ≥60 ml/min) 4. History of confirmed COVID-19 infection (SARS-CoV-2 positive PCR/NAAT, positive antigen, positive nucleocapsid antibodies, or positive spike antibodies before vaccination for SARS-CoV-2) by either documented test result or medical records OR by self-report of positive test (e.g., home rapid antigen test) with clinical and/or epidemiological features consistent with COVID-19 infection (the latter group not to exceed 15% of total study sample size) 5. Post-COVID-19 symptoms persisting greater than three months (>90 days) since the initial COVID-19 infection that caused the Long COVID. Symptoms must be present for more days than not, were not present prior to COVID-19 infection, and are not explained by another cause 6. Patient's post-COVID symptom(s) must be at least 2 of the following 6 core symptoms or symptom clusters: a. Fatigue b. Brain fog (including difficulty with focus, memory, word-finding, processing, orientation, or multitasking) c. Shortness of breath d. Body aches (muscle or joint pain) e. Cardiovascular symptoms (including chest pain, tachycardia, palpitations, or lightheadedness)

	f. Gastrointestinal symptoms (including nausea, vomiting, diarrhea, constipation, abdominal pain, or decreased appetite) 7. Severity of at least two of the core PASC symptom(s) above must be moderate or severe, 2 or 3 on a Likert-scale of 0 to 3 (where 0 is absent, 1 is mild, 2 is moderate, and 3 is severe) 8. Willing to provide vaccination history and report all vaccinations received during the study, if any 9. Women of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception during the treatment period and must agree to continue use of this method for 28 days after the last dose of the study intervention 10. Women of childbearing potential must be agreeable to a urine pregnancy screening test 11. Men whose partners may become pregnant must use adequate contraception during the treatment period and must agree to continue use of this method for 28 days after the last dose of the study intervention 12. Willing and able to adhere to study procedures and available for the duration of the study
Exclusion Criteria	1. Suspected or confirmed pregnancy or breastfeeding 2. Severe liver disease (Child-Pugh class C) 3. Use of the study drug within past 30 days of randomization or planned use of the study drug outside of FDA-authorized indication for the duration of the study 4. Receiving other COVID-19 specific treatments within 30 days of randomization 5. History of hypersensitivity or other contraindication to any components of the study drug 6. Current or expected use of any medications or substances that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4 or have known drug-drug interactions with study drug 7. Use or planned use of any supplements or herbs during study drug administration and potential additional time before and after this period as determined necessary by investigators, unless medically indicated (e.g., for nutrient deficiency) and determined to be safe by investigators 8. Known Human Immunodeficiency Virus (HIV) infection with viral load >50 copies/ml or taking prohibited medications for HIV treatment 9. Suspected or confirmed active SARS-CoV-2 infection within past 30 days 10. New or significant change in dosing as determined by study investigators of immune-modulating or immunosuppressive

	medications within 30 days prior to enrollment until the primary endpoint (10 weeks) has been reached 11. Any other medical condition or concomitant medication/therapy that would compromise the patient's safety or compliance with the study protocol or significantly confound interpretation of the clinical and research tests, as determined by study investigators 12. History of COVID vaccine received within 28 days prior to enrollment or other vaccine (including influenza vaccine, shingles vaccine, etc.) within 14 days of enrollment or planned use of any investigational, authorized, or approved vaccine until the primary endpoint (10 weeks) has been reached 13. Current enrollment in, or discontinuation within the last 30 days from, a clinical trial involving any investigational drug or device, or concurrent enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study 14. Inability to provide informed consent 15. Currently hospitalized
Statistical Considerations	We will evaluate the intention-to-treat (ITT) population, defined as the original treatment assignment groups after randomization, for the primary efficacy analysis. We will also analyze the per-protocol group as supportive evidence for the primary efficacy analysis. We plan to enroll 200 participants total with assumption that 180 participants will complete the follow-up at 10 weeks, i.e., a 10% drop off rate. With a planned randomization ratio of 2:1, we expect approximately 120 participants receiving Paxlovid and 60 participants receiving placebo completing the study. The primary outcome is symptom severity for the 6 core symptoms: fatigue, brain fog, dyspnea, body aches, cardiovascular symptoms, and gastrointestinal symptoms based on Likert-scale score (0, 1, 2, and 3) at 10 weeks. **Statistical hypotheses** for the primary efficacy outcome: • H_0 = There is no difference in the symptom severity in *any* of the 6 core symptoms at 10 weeks between Paxlovid and placebo groups. • H_1 = There is a difference in the symptom severity of *at least* one of the 6 core symptoms at 10 weeks between Paxlovid and placebo groups. For each aforementioned symptom, we plan to use the proportional odds regression model for ordinal outcomes to compare the Likert scale at 10 weeks (stratified by their baseline level) among participants experiencing the corresponding symptoms at the baseline. The overall comparison will be made based on averaging

	regression coefficients from comparisons of individual symptoms weighted by the sample size of the regression analysis, i.e., the number of participants experiencing the corresponding symptom at the baseline. The power estimation is made based on following simplified assumptions: (a) for each symptom, the Likert-scale at week 10 is uniformly distributed over 0, 1, 2, and 3 in the placebo group, i.e., the proportions of the participants with a Likert-scale being 0, 1, 2, and 3 are 25%, 25%, 25%, and 25%, respectively, among all participants in the study including participants without the symptom at the baseline. (b) for each core symptom, the proportions of the participants in the Paxlovid group with a Likert-scale being 0, 1, 2, and 3 are 34.8%, 26.8%, 21.2%, and 17.2%, respectively, among all study participants. (c) The z-scores of comparing 6 symptoms using all participants are positively correlated with a pair-wise correlation coefficient of 0.25. Assumptions (a) and (b) satisfy the proportional odds model with a odds ratio of 1.6. Under this assumption, the z-score of individual comparison based on 60 participants in the placebo group and 120 participants in the Paxlovid group follows a normal distribution with mean of 1.66 and unit variance. The final test statistic is equivalent to the simple average of z-scores from analyses for individual symptoms, since the assumed alternatives are identical for all core symptoms. Under assumption (c) the Wald test statistic for the overall comparison follows a normal distribution with a mean of 2.71 and unit variance, **providing a power of 77% at the two-sided significance level of 0.05**. The proposed test is expected to have a higher power than that of the analysis discussed above for several reasons. First, the regression analysis excluding participants without the core symptom at the baseline is expected to generate a z-score with a greater mean value and a higher power, since the potential dilution effect from participants without the core symptom at the baseline are reduced. Second, the sample size weighting is expected to generate a more efficient combination of test statistics from individual test than equal weighting. Lastly, the stratification by baseline Likert scale will also increase the power of comparing severity of individual symptom and also the power of overall comparison.

1.2 SCHEMA


15-day treatment period
Follow-up period
Adults with PASC (n= 200)
2:1
Nirmatrelvir-Ritonavir (n ≈ 133)
Placebo-Ritonavir (n ≈ 67)
Primary Endpoint (week 10)
Study End
Screening
Baseline
Day 15
Week 5
Week 10
Week 15
Symptoms survey
Weekly
Every 2 Weeks
PROs
Visit 1 (Day 0) PGIS PROMIS surveys
(Day 7) PGIS PGIC
Visit 2 (Day 15) PGIS PGIC PROMIS surveys
Visit 3 (Week 5) PGIS PGIC PROMIS surveys
Visit 4 (Week 10) PGIS PGIC PROMIS surveys
Visit 5 (Week 15) PGIS PGIC PROMIS surveys
Clinical assessments
1-min sit-stand Vital signs Orthostatics
Sample collection
Blood Nasopharyngeal Stool
Stool
Blood Nasopharyngeal
(Digital wearables)
Continuous (optional)

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Screening** Day -14 to 0	**Baseline Day 0**	**Day 7** +/-2 days	**Day 15** +/-2 days	**5 weeks** Day 35 +/-7 days	**Primary Endpoint 10 weeks** Day 70 +/-7 days	**Final Study 15 weeks** Day 105 +/-14 day	Unscheduled Visit[e]
Visits (V1-V5 +/-VU)		**V1**		**V2**	**V3[h]**	**V4**	**V5[h]**	**VU**
Informed consent	X							
Eligibility Assessment	X							
Demographics	X							
Medical history	X							
Randomization	X							
Concomitant medications	X	X ----------X						X
Concomitant supplements	X	X ----------X						X
Treatment								
Administer study intervention		X--------15 days-------X						
Patient-reported outcomes (PROs)								
PASC symptoms (6 core) assessment[a]	X			X---------- weekly ----------X			Q 2 weeks	
PASC symptoms (20 expanded) assessment[a]		X	X	X	X	X	X	(X)
Patient Global Impression of Severity (PGIS) scale		X	X	X	X	X	X	(X)
Patient Global Impression of Change (PGIC) scale			X	X	X	X	X	(X)
PROMIS Physical Function survey		X		X	X	X	X	(X)
PROMIS Fatigue-SF survey		X		X	X	X	X	(X)
PROMIS Dyspnea severity survey		X		X	X	X	X	(X)
PROMIS Cognitive Function Abilities survey		X		X	X	X	X	(X)
Clinical assessments								
1-minute sit-to-stand test		X		X	X	X	X	(X)
Orthostatics		X		X	X	X	X	(X)
Vital signs		X		X	X	X	X	(X)
Safety laboratory monitoring								
Complete blood count[b]	X			X				
Serum chemistry[c,d]	X			X				
Urine pregnancy test		X						
COVID-19 antigen test		X						
Other sample collection for exploratory measures								
D-dimer (blood)		X		X		X		
Other blood collection (for immunologic assays, etc.)		X		X	X	X	X	(X)
Nasopharyngeal swab		X		X	X	X	X	(X)
Stool collection		X	X[f]	X		X		
Other assessments								
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X
Adverse event review		X ----------X						X
Digital wearable sub-study (optional)								
Apple watch		X ---------- (continuous)[g] ----------X						X

Procedures	**Screening** Day -14 to 0	**Baseline Day 0**	**Day 7** +/-2 days	**Day 15** +/-2 days	**5 weeks** Day 35 +/-7 days	**Primary Endpoint 10 weeks** Day 70 +/-7 days	**Final Study 15 weeks** Day 105 +/-14 day	Unscheduled Visit[e]
Blood pressure monitor		X ---------- (daily to biweekly)[g] ----------X						

[a]6 core symptoms are included in the 20 symptoms survey and not collected on the days when 20 symptoms survey is collected. 6 core symptoms assessment is collected every week until the primary endpoint (10 weeks) and then every 2 weeks thereafter until study completion.
[b,c]screening laboratory data can be provided by chart review or patient records if available within the 6 months prior or since index COVID-19 infection data, whichever is the shorter timeframe, assuming no major interval medical events have occurred since those results.
[d]albumin, AST, ALT, total bilirubin, creatinine
[e]if there has been a relevant change in clinical status as determined by investigator and select assessments and specimen collection may be performed per investigator's discretion
[f]home stool collection
[g]target goal data collection schedule detailed in Section 8.8, as able by participant
[h]in-person activities for visits #3 and #5 may be optional for select participants with significant travel or other logistical barriers per investigator's discretion. Relevant electronic PROs will be collected on all participants for all visits.

2 INTRODUCTION

2.1 STUDY RATIONALE

Long COVID or post-acute sequelae of SARS-CoV-2 (PASC) is a major public health crisis in the wake of the ongoing pandemic, with estimates of over 27 million PASC cases in the United States alone as of August, 2022 (7, 8). PASC encompasses various conditions and symptoms, such as fatigue, brain fog, and dyspnea, that develop in about 10-30% of individuals after their initial COVID-19 infection and can last for months or longer with significant impact on quality of life and function (9-11). The underlying mechanisms of disease are unclear and there are currently no known effective therapies to treat PASC. Given the large-scale impact of PASC globally on the individual patient and the broader society and economy, there is an urgency for rigorous and timely evaluation of potential treatments.

2.2 BACKGROUND

Several hypotheses have been proposed to explain the multiple symptoms present in PASC, and one of the leading hypotheses is viral persistence. Several diseases are caused by persistent viral infections including acquired immune deficiency syndrome (AIDS), AIDS-related complexes, chronic hepatitis B and C, Ebola, subacute sclerosing panencephalitis (chronic measles encephalitis), herpes viruses, chronic papovaviral encephalitis (progressive multifocal leukoencephalopathy), spongiform encephalopathies (caused by prions), several herpesvirus-induced diseases, and some neoplasia. The pathogenic mechanisms by which these viruses

cause disease include disorders of biochemical, cellular, immune, and physiologic processes (12-16).

SARS-CoV-2 infection can exhibit prolonged viral RNA shedding up to 83 days in the upper respiratory tract and 126 days in the stool, but no live virus has thus far been isolated from culture beyond day 9 of symptoms (17). Although a human SARS-Cov-2 viral reservoir has not been identified, periodontal pockets have been hypothesized to be potential anatomical sites for the viral reservoir (18). An increasing number of studies have shown the presence and persistence of SARS-CoV-2 virus RNA or particles in various tissues (1, 19-22). In autopsy specimens, Chertow et al., detected persistent SARS-Cov-2 RNA in multiple anatomical sites including the brain for up to 230 days. Those sites were associated with increased inflammatory changes and cytopathological effects (23). The same authors demonstrated different variants in the brain than respiratory tract, implying extrapulmonary tissue replication (23). In some individuals the viral persistence may drive disruption of immune responses, dysbiosis, and PASC symptoms (19, 21, 24). Changes in the bacterial, fungal, and viral gut microbiome have been reported as a consequence of SARS-CoV-19 infection (25). Patients with prolonged symptoms had demonstrated alterations in the composition of the microbiome with higher levels of *Ruminococcus* and *Bacteroides* and lower levels of *Faecalibacterium* (26). We and others have reported cases of patients with PASC whose symptoms improved after Paxlovid administration, highlighting the need to study this antiviral agent in a controlled and well-designed clinical trial (27, 28). Unpublished analysis from 140 patients referred to the Stanford post-COVID-19 demonstrated the most common symptoms were fatigue (86.5%), post-exertional malaise (82.8%), brain fog (81.2%), difficulty sleeping (76.7%), and daytime sleepiness (74.6%) and frequency correlated with the severity of the illness.

This study is a randomized, placebo-controlled trial that is designed to assess the efficacy of an oral antiviral therapy in reducing severity of specific PASC symptoms and explore biological markers of disease and treatment outcomes.

Investigational product: nirmatrelvir-ritonavir (trade name: PAXLOVID™)
Nirmatrelvir is a peptidomimetic inhibitor of SARS-CoV-2 main protease (M^{pro}), also referred to as 3C-like protease ($3CL^{pro}$) or nsp5 protease. Inhibition of SARS-CoV-2 M^{pro} renders it incapable of processing polyprotein precursors, preventing viral replication. Nirmatrelvir is boosted with low-dose ritonavir that slows nirmatrelvir metabolism via inhibition of CYP3A4, and thereby provides higher systemic exposure. Ritonavir has no direct activity against SARS-CoV-2. For this study, the dose and exposure is 300 mg nirmatrelvir plus 100 mg ritonavir PO q12h for 15 days.

Previous human experience: Briefly, the clinical development program has included Phase 1 FIH/PK/DDI studies, and several completed phase 2/3 studies, including EPIC-SR (Standard Risk), EPIC-HR (High Risk), and EPIC-PEP (Post-Exposure Prophylaxis). An ongoing Phase 2 study (NCT05438602) is evaluating the efficacy and safety of a 15-day course of PAXLOVID in immunocompromised patients with symptomatic COVID-19. The EPIC-HR study, a large phase 2-3 double-blind, randomized, controlled trial demonstrated that treatment of symptomatic acute COVID-19 in individuals with high risk for progression to severe disease with Paxlovid had an 89% lower risk of COVID-19-related hospitalization or death (29). In December, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for nirmatrelvir/ritonavir for the treatment of patients: (1) with mild to moderate COVID-19 within five days of symptom onset, and (2) at a high risk of progression to severe disease. In the EPIC-HR

study, the incidence of adverse events that emerged during the treatment period was similar in the two arms (any adverse event, 22.6% with Paxlovid vs. 23.9% with placebo; serious adverse events, 1.6% vs. 6.6%; and adverse events leading to discontinuation of the drugs or placebo, 2.1% vs. 4.2%). Dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) occurred more frequently with Paxlovid than with placebo (29). Results from the aforementioned studies as well as real-world post-authorization use consistently support the safety profile for Paxlovid in the treatment of acute COVID-19 (30-32).

Reference to previously submitted IND application(s) and/or marketed products:
A letter of Cross Reference authorizing the FDA to review Chemistry, Manufacturing and Control Information on **IND 153517** has been provided by the manufacturer Pfizer, Inc. It is filed under Additional Information in this application.

2.3 RISK/BENEFIT ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of nirmatrelvir-ritonavir may be found in the FDA EUA fact sheet (33) and investigator's brochure (IB). The SRSD for ritonavir is the USPI for NORVIR (34).

2.3.1 KNOWN POTENTIAL RISKS

As per drug label and EPIC-HR study (29), adverse events (all grades regardless of causality) in the PAXLOVID group (≥1%) that occurred at a greater frequency (≥5 subject difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%). Additional adverse reaction considerations are also detailed below.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) nirmatrelvir (alias: PF-07321332)		
Emesis	Sporadic emesis was observed at ⩾100 mg/kg/day of PF-07321332 in the 15-day non-human primate (NHP) toxicology study.	AEs will be monitored and participants may receive antiemetics.
Hypertension	Transient increases in systolic, diastolic, and mean blood pressure were observed in the preclinical studies. In Study C4671005 (adults at high risk for severe disease), a small imbalance in 9 participants with reported events of hypertension was reported (1% vs <1%).	Vital signs will be monitored per SoA during the study during any in-clinic visits. All AEs will be monitored in the study. Concomitant medications will also be reviewed for potential new AEs and worsening of the condition.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s): Ritonavir		
Gastrointestinal disturbances (including diarrhea, nausea, vomiting and abdominal pain)	Frequently reported adverse reaction in HIV-positive patients who are HIV-positive at 600 mg BID.	Lower dose of 100 mg twice daily is used in this study. There will be close observation of AEs. In addition to ongoing review of AEs by the sponsor, a DSMB will review safety data as described in Section 10.1.6. Taking study intervention with food may improve tolerability.
Neurological disturbances (eg, paresthesia, including oral paresthesia, dysgeusia and dizziness)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs. In addition to ongoing review of AEs by the sponsor, a DSMB will review safety data as described in Section 10.1.6.
Rash (most commonly reported as erythematous and maculopapular, followed by pruritic)	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs and monitoring through targeted clinical exams. If needed, therapeutic interventions per SoC may be provided.
Fatigue/Asthenia	Frequently reported adverse reaction in patients who are HIV-positive at 600 mg BID.	Lower dose used in this study. There will be close observation of AEs. Fatigue will be assessed through regular symptoms surveys and will also be assessed through targeted clinical examinations when performed during the study visits.

2.3.2 KNOWN POTENTIAL BENEFITS

Benefits to individual participants may include:

- Receipt of a potentially efficacious PASC treatment

• Access to COVID-19 diagnostic testing
• Contributing to research to help others in a time of a public health crisis given the millions globally impacted by PASC

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Taking into account the current COVID-19 global pandemic with millions around the world impacted by PASC and the high burden on individuals, healthcare systems, and society at large, the complete lack of readily available and effective treatment options, the safety data on the interventional product, and the measures taken to minimize risk to participants in this study, the potential risks identified in association with nirmatrelvir-ritonavir are justified by the anticipated benefits that may be afforded to participants with PASC. An independent DSMB will be responsible for monitoring the safety of participants at regularly scheduled intervals throughout the duration of the study and for assessing safety and futility using conditional power at the time of the interim analysis according to the DSMB charter.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To compare the efficacy of a 15-day course of Paxlovid versus placebo in reducing symptom(s) severity of participants with PASC	Core symptoms severity based on Likert-scale score at 10 weeks in participants treated with Paxlovid versus placebo. Core symptoms defined as: fatigue, brain fog, dyspnea, body aches, gastrointestinal symptoms, cardiovascular symptoms	The primary endpoint was chosen for the following considerations: clinically meaningful, patient-centered, accounts for heterogeneous spectrum of PASC while focusing on symptoms that are most prevalent, most disruptive to patients, and most likely to be proximal in the hypothesized disease mechanism targeted by intervention (without knowing *a priori* which symptom(s) may be most impacted, if any). The timing of

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		the primary endpoint was selected to ensure sufficient follow-up after treatment to assess durability of response (if any) while also considering public health urgency of study and potential for confounding events to occur as time elapses.
Secondary		
To compare other measures of symptoms severity and overall symptom burden of participants with PASC treated with Paxlovid versus placebo To identify which core PASC symptom(s) are most responsive to Paxlovid treatment, if any	• Core symptoms severity based on Likert-scale score at 15 days in participants treated with Paxlovid versus placebo • • Proportion of participants reporting relief at 10 weeks of at least one core symptom for 2 weeks. Relief defined as reduction of severity from moderate to none or severe to mild/none, ≥2-point Likert score change from baseline • Proportion of participants with overall alleviation at 10 weeks in Paxlovid versus placebo group for 2 weeks. Overall alleviation defined as both: (1) any core symptom(s) that are none/mild (Likert 0 or 1) at baseline are none at 10 weeks and (2) any core symptom(s) that are moderate/severe (Likert 2 or 3) at baseline are none/mild at 10 weeks • Severity of the most bothersome symptom, designated by patient at baseline, at 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group •Time to relief of each of the 6 core symptoms. Relief defined as above.	Other measures of patient-reported symptoms such as summative symptom burden, proportion of participants achieving relief, and time-to-relief are also clinically meaningful efficacy measures and may be responsive to the intervention that offer additional support to effect of intervention. Additional secondary endpoints were also chosen to assess each of the core symptoms individually to identify best responders who may be enriched in enrollment in follow-on studies.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To evaluate other patient-reported outcomes (e.g., functional status, global health status, etc.) in participants with PASC treated with Paxlovid versus placebo	• Change in PROMIS Physical Function SF 4a v2.0 from baseline to 10 weeks • Change in PROMIS Fatigue SF 7a v1.0 score between baseline and 10 weeks • Change in PROMIS Dyspnea-Severity SF 5a v1.0 score between baseline and 10 weeks • Change in PROMIS Cognitive Function Abilities score between baseline and 10 weeks • Patient Global Impression of Severity scale (PGIS) at 15 days, 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group • Patient Global Impression of Change scale (PGIC) at 15 days, 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group	Given the paucity of PASC-specific PROs, these broadly used and validated PROs were chosen as secondary efficacy measures and to correlate with PASC symptoms assessments in global or specific domains.
To evaluate clinical measures related to core symptoms in participants with PASC treated with Paxlovid versus placebo	• Change in orthostatic vitals (difference in seated versus standing blood pressure and heart rate) from baseline and 10 weeks • Change in 1-minute sit-stand test from baseline and 10 weeks	These are potential objective surrogate clinical measures of efficacy outcomes that match core PASC symptom domains and deficits.
Exploratory		
To investigate potential biological biomarkers of PASC in participants treated with Paxlovid versus placebo	• Clinical laboratory tests including d-dimer • Stool RNA RT-qPCR to assess for presence of SARS-CoV-2 at baseline, 7 days, 15 days (immediately after treatment), 10 weeks (1) • Difference in drug versus placebo and change from baseline of: o O-link cytokine profiles, specific chemokines such as CCL11, others (2) o Autoantibodies – bead-based, multiplexed assays (3, 4)	There are no known biological markers of PASC or PASC severity. These exploratory measures were chosen based on mechanistic rationale related to viral and immunological factors that may be associated with PASC and respond to the study intervention, allowing

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	○ Bulk RNA-Sequencing (5) ○ Anti-SARS-CoV-2, EBV, CMV and other IgG responses, measured in a combined panel of autoantibodies described above (3) ○ Proportion of blood cells measured by flow cytometry, including anti-SARS-CoV-2 T cell responses measured using spheromers (6) • Other assays that may emerge regarding PASC pathophysiology	exploration of new hypotheses of underlying disease mechanisms and identification of novel and objective biomarkers of disease.
To investigate potential digital biometric markers of PASC symptom severity and correlate with intervention outcomes *(substudy)*	• Change in digital wearable biometric measures over time in drug versus placebo groups for: ○ Physical activity (PA) measured by hand accelerometer ○ Ratio of daytime versus nighttime PA level ○ Time asleep and time in bed ○ Heart rate and resting heart rate ○ Heart rate variability ○ ECG rhythm abnormalities ○ O_2 saturation ○ Blood pressure	These physiological and behavioral biometric endpoints were chosen as correlates to symptom domains (e.g., cardiovascular, dyspnea, fatigue) and to explore additional objective measures of PASC severity and functional debilitation.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a phase 2, single-center, randomized, double-blind, placebo-controlled pilot trial to evaluate the efficacy and safety of nirmatrelvir-ritonavir (Paxlovid) in treating PASC in adults and to explore potential biological and digital wearable biometric markers of disease. A total of 200 participants with PASC who meet all the inclusion criteria will be randomized 2:1 to a 15-day course of twice-daily (a) Paxlovid (nirmatrelvir 300 mg – ritonavir 100 mg), or (b) placebo (placebo 0 mg – ritonavir 100 mg). A total of ~133 and ~67 participants will be enrolled in the two arms above, respectively. Randomization will be stratified by the number of moderate or

severe core symptoms (2 or 3 vs >3) and vaccination status (completed primary series vs not completed as defined by CDC (35)). The randomization list for each stratum will be generated by block randomization with block size randomly selected from 6 and 9. Symptoms severity assessments, patient-reported outcomes (PROs), clinical assessments, and specimen collection will be performed at the time points shown in SoA.

Hypothesis: Adult PASC patients treated with Paxlovid for 15 days will report reduced PASC symptoms severity at 10 weeks compared to placebo.

Interim analysis is planned and detailed in Section 9.4.6 "Planned Interim Analysis."

Sub-study: An exploratory sub-study will investigate the correlation of physical activity and biometric parameters from digital wearable devices with the subjective symptom severity and other patient-reported outcomes in the main study. All participants with iPhone 6S Plus or newer will be offered an opportunity to opt-in to this study. An Apple Watch and Bluetooth-enabled blood pressure monitor will be provided to participants and data will be collected for the duration of the main study to track participants' physiological and behavioral trends in the Paxlovid versus placebo groups. About 100-120 participants are expected to enroll into the substudy based on regional iPhone use rates.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

General considerations: There are currently major challenges facing any clinical trial designed to address interventions in PASC: (1) There is not a precise clinical definition of PASC and it is currently defined by a time-frame rather than specific clinical criteria or diagnostic test, (2) heterogeneity is a hallmark of this condition, (3) there are no known biomarkers or other objective measures of PASC or PASC severity, (4) the underlying disease mechanism(s) is/are unclear, (5) there are no standard eligibility criteria or standard endpoints for PASC trials, and (6) there are no validated, disease-specific symptom assessment tools that have been used in published clinical research studies for PASC. This trial was designed with these limitations in mind and comprises significant exploratory components that will help address these gaps in knowledge and inform follow-on studies.

Specific considerations:
Placebo arm – The study intervention is nirmatrelvir that is pharmacologically boosted by low-dose ritonavir. The ritonavir has no activity against SARS-CoV-2 but accounts for the dysgeusia that is reported in a small percentage of individuals who take nirmatrelvir-ritonavir (29). In order to avoid unblinding to the participant based on this side effect, the placebo arm is a placebo (matched to nirmatrelvir) given with ritonavir. The current standard of care for PASC is based on expert consensus recommendations of supportive lifestyle measures such as pacing, healthy diet, etc. There are no known effective therapeutic interventions for PASC.

Patient population – The eligibility criteria were selected with consideration of balancing inclusivity and precision, prioritizing safety (e.g., drug-drug interactions), and taking into account significant confounding factors that will impact interpretation of outcomes (e.g., acute infections, vaccinations, certain comorbidities, etc.)

Randomization ratio – Although a 1:1 ratio would have been selected under the assumption of equipoise, based on our experience with PASC patients, we anticipate that many participants may not want to have a 50% chance of being randomized to placebo given the significant debilitation of PASC in many individuals and their urgency to find effective therapies. We, therefore, increased the ratio (2:1 drug:placebo) to reduce the chance of being randomized to placebo to 33% to mitigate potential enrollment barriers.

Randomization stratification variables – Total core symptom burden and vaccination history are likely to influence treatment responsiveness and, therefore, randomization will be stratified by these variables in a binary fashion to ensure balance in the treatment groups with respect to each of these variables.

Endpoints – See Section 3 “Objectives and Endpoints” for details on justifications of primary, secondary, and exploratory endpoints.

Duration of treatment and follow-up – These timeframes were determined based on considerations of existing safety data, the chronicity of PASC, and also reported potential rebound of symptoms in the acute COVID-19 treatment setting (36).

4.3 JUSTIFICATION FOR DOSE

An oral dosing regimen of 300 mg nirmatrelvir administered with 100 mg ritonavir q12h administered orally for 15 days will be evaluated in this study. Dose selection for this study included consideration of all relevant available preclinical and clinical data, including repeat-dose toxicology studies, clinical safety, and PK data from Phase 1 study and *in vitro* pharmacology studies with nirmatrelvir.

The selected duration is based on effectiveness of 5-day administration of study drug used in treatment of acute SARS-CoV-2 and the hypothesized need for longer duration in treatment of a persistent viral reservoir causing chronic symptoms. Additionally, there is consideration of potential rebound symptoms that have been reported for the 5-day course (36). Safety data from the Phase 1 dosing study in humans included well-tolerated use at 750 mg nirmatrelvir with 100 mg ritonavir q12h for 10 days which is higher dosing than in this study (30). There is also currently an ongoing clinical trial evaluating nirmatrelvir-ritonavir 300mg-100mg q12hr up to 15 days for treating COVID-19 in adults and adolescents who are immunocompromised (NCT05438602). Please see above Section 2.2 Background regarding previous human experience.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of

Activities (SoA), or has withdrawn from the study, or is lost to follow-up as defined in Section 7.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Adults 18 years and older
2. Weight > 40 Kg
3. Normal or near-normal renal function (eGFR ≥60 ml/min based on CKD-EPI formula as per drug label)
4. History of confirmed COVID-19 infection (SARS-CoV-2 positive PCR/NAAT, positive antigen, positive nucleocapsid antibodies, or positive spike antibodies before vaccination for SARS-CoV-2) by either documented test result or medical records OR by self-report of positive test (e.g., home rapid antigen test) with clinical and/or epidemiological features consistent with COVID-19 infection (the latter group not to exceed 15% of total study sample size)
5. Post-COVID-19 symptoms persisting greater than three months (>90 days) since the initial COVID-19 infection that caused the Long COVID. Symptoms must be present for more days than not, were not present prior to COVID-19 infection, and are not explained by another cause
6. Patient's post-COVID symptom(s) must be at least 2 of the following 6 core symptoms or symptom clusters:
    a. Fatigue
    b. Brain fog (including difficulty with focus, memory, word-finding, processing, orientation, or multitasking)
    c. Shortness of breath
    d. Body aches (muscle or joint pain)
    e. Cardiovascular symptoms (including chest pain, tachycardia, palpitations, lightheadedness)
    f. Gastrointestinal symptoms (including nausea, vomiting, diarrhea, constipation, abdominal pain, decreased appetite)
7. Severity of at least two of the core PASC symptom(s) above must be moderate or severe, 2 or 3 on a Likert-scale of 0 to 3 (where 0 is absent, 1 is mild, 2 is moderate, and 3 is severe)
8. Willing to report all vaccinations received prior to and during the study, if any
9. Women of childbearing potential (not surgically sterile or 2 years postmenopausal) must use a medically accepted method of contraception during the treatment period and must

agree to continue use of this method for 28 days after the last dose of the study intervention
10. Women of childbearing potential must be agreeable to a urine pregnancy screening test
11. Men whose partners may become pregnant must use adequate contraception during the treatment period and must agree to continue use of this method for 28 days after the last dose of the study intervention
12. Willing and able to adhere to study procedures and available for the duration of the study

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Suspected or confirmed pregnancy or breastfeeding
2. Severe liver disease (Child-Pugh class C)
3. Use of the study drug within past 30 days of randomization or planned use of the study drug outside of FDA-authorized indication for the duration of the study
4. Receiving other COVID-19 specific treatments within 30 days of randomization
5. History of hypersensitivity or other contraindication to any components of the study drug
6. Current or expected use of any medications or substances including supplements and herbs that are highly dependent on CYP3A4 for clearance or are strong inducers of CYP3A4 or have known drug-drug interactions with study drug
7. Use or planned use of any supplements or herbs during study drug administration and potential additional time before and after this period as determined necessary by investigators, unless medically indicated (e.g., for nutrient deficiency) and determined to be safe by investigators
8. Known Human Immunodeficiency Virus (HIV) infection with viral load >50 copies/ml or taking prohibited medications for HIV treatment
9. Suspected or confirmed active SARS-CoV-2 infection within past 30 days
10. New or change in the dosing of immune-modulating or immunosuppressive medications within 30 days prior to enrollment until the primary endpoint (10 weeks) has been reached
11. Any other medical condition or concomitant medication/therapy that would compromise the patient's safety or compliance with the study protocol or significantly confound interpretation of the clinical and research tests, as determined by study investigators
12. History of COVID vaccine received within 28 days prior to enrollment or other vaccine (including influenza vaccine, shingles vaccine, etc.) within 14 days of enrollment or planned use of any investigational, authorized, or approved vaccine until the primary endpoint (10 weeks) has been reached
13. Current enrollment in, or discontinuation within the last 30 days from, a clinical trial involving any investigational drug or device, or concurrent enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
14. Inability to provide informed consent
15. Currently hospitalized

5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an easily modifiable factor (e.g., over-the-counter supplement use) or temporary factor (e.g., positive COVID-19 rapid antigen test) may be rescreened at a later time. Rescreened participants should be assigned the same participant number as for the initial screening.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment: We will employ the following tiered recruitment and screening strategy for our target enrollment of 200 participants total in this single-center trial:

1. We will directly recruit from our Stanford PASC clinic ("Post-Acute-COVID-19 Syndrome Clinic") which follows over 300 patients with PASC and from the long clinic waitlist.
2. We will recruit from our multiple Stanford research cohorts including patients whom we have followed long-term after their initial acute COVID-19 infection.
3. We will recruit through our Stanford Healthcare network of healthcare professionals who may care for or know someone with PASC.
4. We will recruit through our PASC physician colleagues who lead regional post-COVID care centers (e.g., UCSF and UC Davis).
5. We will recruit through physical and web-based flyers, advertisements including via social media outlets and patient advocacy groups. Recruitment materials will be available in Spanish and potentially other languages and posted to community clinics to promote diversity in enrollment and outreach to historically underrepresented populations.
6. We will screen interested participants with direct phone calls with our study team to assess eligibility criteria. We will also utilize a pre-screening self-referral web tool to allow more efficient in-flow into our formal screening process.

Specific strategies to recruit diverse populations: Patient-facing materials including study advertisements, recruitment materials, patient self-referral form, etc. will be translated to Spanish. Additionally, there will be direct outreach to community clinics and county medical centers that serve diverse and historically underrepresented populations.

Retention: Participants will be engaged in the study through multiple channels including:

- Compensation for participants during each study visit
- Visit reminders and multiple contact methods to participants by our clinical research coordinators (CRCs)
- Developing participant-centered approaches that recognize the needs and preferences of individuals with PASC

- Multifaceted approaches that combine engagement tools, education, effective communication, online systems, social media, and advocacy resources.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol. For the purposes of this protocol, study intervention refers to: nirmatrelvir (PF-07321332) 150 mg tablets with ritonavir 100 mg capsules or matching placebo with ritonavir 100 mg capsules. Nirmatrelvir or placebo will be 150 mg Oval Pink Coated Tablets that will be packaged in a blister pack while ritonavir consists of capsules stored in a bottle. The participant will receive 3 blister packets and 3 bottles of ritonavir.

Intervention Name	Nirmatrelvir	Placebo for nirmatrelvir	Ritonavir
ARM Name (group of patients receiving a specific treatment (or no treatment))	Nirmatrelvir-Ritovanir (Paxlovid)	Placebo	Both arms
Type	drug	placebo	drug
Dose Formulation	tablet	tablet	capsule
Unit Dose Strength(s)	150 mg	0 mg	100 mg
Dosage Level(s)	300 mg q12h for 15 days	0 mg q12h for 15 days	100 mg q12h for 15 days
Route of Administration	oral	oral	oral
Use	experimental	placebo	experimental/control
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided by Pfizer, Inc.	Provided by Pfizer, Inc.	Provided by Pfizer, Inc.
Packaging and Labeling	Study intervention will be provided in blister wallets. Each wallet will be labeled as required	Study intervention will be provided in blister wallets. Each wallet will	Study intervention will be provided in HDPE bottles. Each bottle will

	per country requirement. Products will be provided with blinded labels.	be labeled as required per country requirement.	be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Nirmatrelvir PF-07321332	N/A	ritonavir

6.1.2 DOSING AND ADMINISTRATION

Nirmatrelvir 150 mg tablets or placebo for nirmatrelvir, will be administered for 15 days with ritonavir 100 mg capsules. Participants will be dispensed 1 blister wallet of PF-07321332 150 mg or placebo for PF-07321332 tablets and 1 bottle of ritonavir capsules. Participants will be given clear dosing instruction to take:

- 2 tablets of nirmatrelvir 150 mg or placebo q12h
- 1 capsule of ritonavir 100 mg q12h

Participants should take nirmatrelvir/placebo and ritonavir at the same time (no more than 15 minutes apart). The study intervention should be taken every 12 hours (±4 hours), and not more than twice in a calendar day. Participants should take the first dose of the study intervention on Day 0. Depending on the time of first dose, the timing of the subsequent dose may be adjusted slightly to allow the participant/caregiver to select a convenient 12 hour dosing schedule as long as the next dose is taken at least 4 hours, but no later than 16 hours, after the previous dose. Once adjusted, all subsequent doses should be taken every 12 hours (±4 hours).

If a dose is delayed, it should be taken as soon as possible (but no later than 8 hours after the scheduled 12-hourly dose time), then resume the normal dosing schedule. If the participant misses a dose by more than 8 hours, the participant should not take the missed dose and instead take the next dose at the regularly scheduled time. The participant should not double the dose to make up for a missed dose. Dosing should be stopped at the end of the treatment period (Day 15 or 16). Any remaining tablets and/or capsules at the Day 15 visit should be returned. If the Day 15 visit is conducted prior to the last dose of study intervention (i.e., Day 16), any remaining tablets or capsules should be collected at the next visit.

If a participant experiences difficulty swallowing the ritonavir capsule, the study team will provide guidance on multiple strategies to facilitate swallowing the full-sized capsule. If these strategies are unsuccessful, the study team may guide the participant to carefully remove the outer encapsulation and take the intact ritonavir tablet that is contained within the encapsulation. The outer encapsulation will be discarded.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

IDS will receive delivery of study intervention and control product from manufacturer, Pfizer, Inc. Study drug accountability and monitoring will be performed by the Stanford Health Care Investigational Drug Service (IDS). IDS will maintain accurate, complete, and current records of receipt, use, or disposition of study drugs, including: 1) dates of receipt, 2) dates of dispensing, 3) quantities currently maintained for dispensing, 4) name of participant and amount dispensed, and 4) amounts remaining at the end of trial and method of disposition.

All study interventions will be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. 6) Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

See section 6.1.1 Study Intervention Description for details on formulation, packaging, and labeling.

6.2.3 PRODUCT STORAGE AND STABILITY

Medications will be stored at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized 2:1 to drug:placebo. Allocation of participants to treatment groups will be conducted in the study's electronic data capture platform, REDCap Cloud. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a container number(s) to indicate the drug product to be supplied to the patient.

The randomization allocation will be generated before the first patient is enrolled and uploaded into REDCap Cloud by the unblinded biostatistical team. The unblinded biostatisticians will store the randomization allocation in a directory that is inaccessible to blinded personnel.

Study intervention will be dispensed at the study visits summarized in the SoA. Returned study intervention will be disposed immediately by study staff and must not be re-dispensed to the study participants.

The participant, treating clinicians, and study personnel will remain blinded to study drug versus placebo assignment until after the database is locked and blinded analysis is completed. Only the biostatistical team who is generating the randomization allocation and preparing closed DSMB interim reports will be unblinded. Specifically, study drug/placebo will be dispensed with packaging and labelling that would blind treatment assignment. Unblinding will occur only if required for participant safety or treatment at the request of the treating clinician. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

6.4 STUDY INTERVENTION COMPLIANCE

Study intervention compliance will be assessed by delegated site personnel through the accounting of unused study intervention returned by the participant at the study visits and discussion with the participant. Participants will also be asked during the 15-day treatment period to log their doses taken and missed with their symptom survey every 5 days. Study intervention administration, including any deviation(s) from the prescribed dosage regimen, should be recorded in the CRF. A record of the number of study intervention tablets/capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates will also be recorded in the CRF.

The following noncompliance cases will be considered medication errors (see Section 8.3.10):

- Participants interrupting study intervention for 4 consecutive doses;
- Participants taking either nirmatrelvir or ritonavir alone for 4 consecutive doses;
- Participants who have an overall study intervention compliance of <80% or >115%.

In addition to the above-listed medication errors, any deviation from protocol specified dosing (e.g., missed single dose or partial dose) should be recorded as a protocol deviation and the investigator or designee is to counsel the participant and ensure steps are taken to improve compliance.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, herbs, and supplements.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 2).

Permitted During the Study

All participants may receive standard of care (SoC) therapy for acute COVID-19 re-infection if they qualify under the current emergency use authorization (EUA) indications, unless listed as prohibited medication on latest FDA Paxlovid Fact Sheet or as defined in Section 5.2. SoC therapy is defined as any therapy that is approved and used as indicated by the local regulatory authorities (including approvals for emergency use, compassionate use, or through similar regulatory guidance), or any therapy as recommended by a relevant national (or a reputable international) scientific body (eg, WHO, ECDC, CDC, NIH). Investigator will ensure that any recommended SoC therapy is not a strong inducer of CYP3A4 or highly dependent on CYP3A4 for clearance.

Prohibited During the Study
Nirmatrelvir and ritonavir are both primarily metabolized by CYP3A4. Therefore, concomitant use of any medications or substances that are strong inducers of CYP3A4 and that are contraindicated in combination with nirmatrelvir/ritonavir are prohibited without the appropriate washout prior to the first dose of study intervention.

Additionally, nirmatrelvir and ritonavir are inhibitors of CYP3A4. Therefore, medications highly dependent on CYP3A4 for clearance and for which elevated plasma concentrations may be associated with serious and/or life-threatening events are not permitted during dosing of nirmatrelvir-ritonavir and for 4 days after the last dose of nirmatrelvir-ritonavir. Because ritonavir 100 mg every 12 hours is being used to boost the exposure of nirmatrelvir, no additional DDIs are expected other than those associated with ritonavir 100 mg q12h based on *in vitro* assessments of nirmatrelvir.

A nonexhaustive list of prohibited and precautionary medications is provided on the latest FDA Paxlovid Fact Sheet for Prescribers (FDA.gov), which may be further updated and revised during the course of the study. If a medication is not listed, it should not automatically be assumed it is safe to coadminister. Appropriately qualified site staff will review all concomitant medications (prescription medications, over-the-counter medications, herbs, and supplements) during pre-screening intake, during screening, and before the first dose of study intervention is administered to determine if they are prohibited. The investigator will make a judgement on the ongoing participation of any participant with prohibited medication use during the study.

At least two qualified study team members must independently review all concomitant medications before the first dose of study intervention is administered. Participants should not stop any medically-necessary medications and, therefore, will be ineligible to participate in the study if they are on such medications that are both medically-necessary for comorbid condition(s) and prohibited in the study. Participants who are on *non*-essential prohibited medications may stop these medications to participate in the study at the discretion of their prescribing clinician with appropriate wash-out period if needed and resumption timeline after completion of study drug.

Due to safety concerns regarding supplements and herbs and potential interactions with the study drug, use or planned use of any supplements or herbs during study drug administration and potential additional time before and after this period as determined necessary by

investigators is prohibited, unless medically indicated (e.g., for nutrient deficiency) and determined to be safe by investigators.

Vaccination: COVID vaccination is prohibited within 28 days prior to enrollment. Other types of vaccination (including COVID vaccine, influenza vaccine, shingles vaccine, etc.) are prohibited within 14 days prior to enrollment. Planned use of any investigational, authorized, or approved vaccine (including for COVID, influenza, and others) during the duration of the study through the primary endpoint (10 weeks) is also part of the exclusion criteria for the trial (see Section 5.2), but all participants may receive vaccinations including COVID-19 vaccination as part of SoC indications if their plans and intentions have changed since screening.

Immune-related medications: New or significant change in the dosing of immune-modulating or immunosuppressive medications as determined by investigators are prohibited within 30 days prior to enrollment and through the primary endpoint (10 weeks).

6.5.1 RESCUE MEDICINE

Standard medical supportive care may be provided to manage AEs.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following.

- AE (including Grade 3 severity or greater and considered by the investigator to be related to study intervention);
- SAE considered by the investigator to be related to the study intervention;
- Requirement for prohibited concomitant medication;
- Death;
- Pregnancy;
- Study terminated by sponsor;
- Withdrawal by participant or legally authorized representative
- Hospitalization during the active treatment period;
- Miss more than 4 consecutive doses of study intervention.
- Determination by the study team that the participant cannot appropriately participate in the study

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant will remain in the study to be

evaluated for all subsequent scheduled assessments. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed. In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.1.1 POTENTIAL CASES OF DECREASED EGFR

If post-screening eGFR is <60 ml/min/1.73 m^2 the participant will be instructed to discontinue any remaining study intervention dose*s* as soon as study staff become aware of laboratory results.

7.1.2 POTENTIAL COVID-19 REINFECTION

If a participant is acutely infected with SARS-CoV-2 during the 15-day treatment period, and they meet criteria for EUA treatment of acute COVID-19 (e.g., high risk for severe infection), the participant will be offered unblinding in order to obtain standard of care.

If a participant is acutely infected with SARS-CoV-2 more than 5 days after the 15-day treatment period, and they meet criteria for EUA treatment of acute COVID-19 (e.g., high risk for severe infection), the participant will be offered a 5-day course of Paxlovid, which is consistent with current standard of care.

If a participant is acutely infected with SARS-CoV-2 during the trial duration and is not eligible for acute COVID-19 treatments (e.g., he/she is at low risk for severe Covid-19 infection) according to standard of care, the investigator will recommend that they continue in the study without unblinding and no SARS-CoV-2 therapy will be offered.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention or study procedure non-compliance
- If any clinical adverse event (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
- Disease progression which requires discontinuation of the study intervention

- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention for 4 consecutive days.
- Study terminated by sponsor

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form (ICF) and are randomized but do not receive the study intervention will not be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study 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 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.
- 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 medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 PASC SYMPTOMS ASSESSMENT

6 "core" PASC symptoms or symptom categories of interest are defined in table below and were selected based on a combination of three primary factors: (1) prevalence in patients with PASC based on the literature (9, 37, 38) and our clinic cohort data, (2) severity of these symptoms in patients with PASC based on our clinic cohort data, and (3) relevance to a putative viral persistence mechanism that would be targeted by the intervention drug. This primary efficacy assessment is also based on published FDA guidance statements on drug intervention trials for

acute COVID-19 and chronic fatigue syndrome/myalgic encephalomyelitis including assessment of key symptoms and symptom clusters on a 4-point scale (39, 40).

20 expanded PASC symptoms encompass the 6 core symptoms, including expanded symptom categories of cardiovascular and gastrointestinal symptoms, and additionally encompass symptoms that are either highly prevalent (e.g., difficulty sleeping) or less prevalent but more likely to be associated with a viral persistence mechanism (e.g., fever). There are hundreds of symptoms that have been associated with PASC, and the only validated PASC-specific symptom survey instrument currently available is the SBQ-LC which is composed of 17 independent scales with over 100 items total and has not yet been used in published studies (41). This study's selected symptoms are all contained in the SBQ-LC questionnaire, which similarly asks respondents to rate their symptom burden at its worst during the past seven days with a 4-point rating scale.

The severity of the symptoms will be assessed on a 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) with participants reporting the severity at its worst over the past 7 days. The 6 core symptoms will be assessed at (1) screening to determine eligibility, (2) every week until the primary endpoint at 10 weeks, and (3) every 2 weeks until the end of the study at 15 weeks. The 20 core symptoms will be assessed at each of the 5 in-person visits: baseline, V1, V2, V3, V4, V5, and during any unscheduled visits as shown in SoA. Because the 6 core symptoms are contained within the 20 expanded symptoms, the 6 core symptoms survey will not be redundantly collected during the in-person visits or Day 7 when the 20 expanded symptoms are assessed. At enrollment, participants will be asked to select their one most bothersome symptom from the expanded 20 symptoms list.

PASC Symptoms Assessed

*Participants will be asked, "For each symptom below, please indicate how severe it was for you **at its worst in the last 7 days**. Please answer ALL the questions."*

		0 none	1 mild	2 moderate	3 severe
1	**Fatigue*** (low energy, tiredness, or exhaustion)				
2	**Brain Fog*** (including difficulty with focus, or memory, or word-finding, or processing, or orientation, or multitasking)				
3	**Shortness of breath*** (including difficulty breathing, or feeling breathless, or air hunger)				
4	**Body aches*** (including pain in joints or muscles)				
5	**Heart symptoms*** (including chest pain, or dizziness, or heart racing, or fast heart rate, or palpitations)				
6	**Gastrointestinal symptoms*** (including nausea, vomiting, diarrhea, constipation, abdominal pain, or decreased appetite)				
7	Post-exertional malaise (worsening of symptoms or feeling unwell after physical or mental activity)				
8	Headache				
9	Cough				
10	Fever (mild <101 deg F; moderate 101-103 deg F; severe >103F)				

11	Sore Throat				
12	Difficulty Sleeping				
13	Chest pain				
14	Heart racing (fast heart rate or palpitations)				
15	Dizziness (including lightheadedness or feeling faint)				
16	Nausea or vomiting				
17	Diarrhea				
18	Constipation				
19	Abdominal pain				
20	Decreased appetite				

6 core symptoms (assessed weekly until primary endpoint at 10 weeks then every two weeks thereafter until study end);
20 expanded symptoms which includes the 6 core symptoms (assessed at each of the 5 in-person visits and day 7 as shown in SoA)

8.1.2 PATIENT REPORTED OUTCOMES (PRO)

This study will utilize patient-reported outcomes (PRO) in electronic format at each of the 5 scheduled visits. PROs are valuable tools to collect patient-centered data and provide unique information on the impact of the intervention from the patient's perspective (42). The PROs were selected to capture both global and symptom domain-specific outcomes.

8.1.2.1 PGIC AND PGIS

The self-report measure Patient Global Impression of Change (PGIC) reflects a participant's perception about the overall efficacy of treatment and their overall status since the start of the treatment. It is widely used in chronic pain clinical trials and has been used as a co-primary or key secondary outcome for trials in conditions with similar features to PASC such as fibromyalgia (43, 44). PGIC is a 7-point scale depicting a patient's rating of overall health status improvement. Patients rate their change as "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse." The PGIC will be assessed on Day 7, Day 15, Week 5, Week 10, and Week 15.

The related self-report measure Patient Global Impression of Severity (PGIS) reflects a participant's perception about the overall severity of their disease symptoms at that time on a 6-point scale (45, 58). PGIS in this study is asked in regards to the overall severity of their Long COVID symptoms rated as "not present," "very mild," "mild," "moderate," "severe," or "extremely severe." The PGIS will be assessed on Day 0 and in parallel with the PGIC on Day 7, Day 15, Week 5, Week 10, and Week 15.

8.1.2.2 PROMIS FATIGUE

Patient-Reported Outcomes Measurement Information System (PROMIS) instruments are a set of highly reliable, widely used, publicly available, and precise tools used to measure patient-

reported health symptoms and health-related quality of life domains relevant to many diseases including chronic conditions. PROMIS instruments are accessible through the HealthMeasures website (47) and are available for use in clinical research and care.

The PROMIS Fatigue-Short Form v1.0 7a (PROMIS Fatigue SF) is a reliable and validated instrument across diverse clinical populations (48, 49). The PROMIS Fatigue SF consists of 7 items that measure both the patient-reported experience of fatigue and the interference of fatigue on daily activities over the past week with each item scored on 5-point Likert scale. The PROMIS Fatigue SF instrument will be administered on the visit days as detailed in SoA for all participants.

8.1.2.3 PROMIS DYSPNEA

The PROMIS Dyspnea Severity Short Form v1.0 5a (PROMIS Dyspnea Severity) is part of the set of PROMIS dyspnea instruments that have been used across different clinical populations including in the post-COVID-19 setting (50). The PROMIS Dyspnea Severity 5a consists of 5 items scored on 4-point Likert scale with a 7-day recall period. The PROMIS Dyspnea Severity instrument will be administered on visit days as detailed in the SoA for all participants.

8.1.2.4 PROMIS COGNITIVE FUNCTION ABILITIES

The PROMIS Cognitive Function Abilities Short Form v2.0 4a (PROMIS Cognitive Function Abilities) is a brief, standardized, reliable, and validated test of self-perceived cognitive functioning in various clinical populations (51, 52). The PROMIS Cognitive Function Abilities consists of 4 items scored on 5-point Likert scale with a 7-day recall period. The PROMIS Cognitive Function Abilities instrument will be administered on visit days as detailed in the SoA for all participants.

8.1.2.5 PROMIS PHYSICAL FUNCTION

The PROMIS Physical Function Short Form v2.0 4a (PROMIS Physical Function) is part of the PROMIS Physical Function question bank of variable-length instruments that have been used across different clinical populations and different levels of ability (57). The Short Form 4a is a concise fixed-length form that assesses difficulty level performing activities of daily living such as doing chores, climbing stairs, walking, and running errands on a 5-point scale (46). The PROMIS Physical Function instrument will be administered on visit days as detailed in the SoA.

8.1.3 CLINICAL ASSESSMENTS

8.1.3.1 1 MINUTE SIT-TO-STAND TEST

The 1 minute sit-to-stand test is a widely used clinical assessment to evaluate exercise tolerance and involves an armless chair and the performance of as many sit-to-stand actions as possible in 1 min without using the upper limbs (53). It will be assessed on all participants at the select in-person visits as shown in the SoA.

8.1.3.2 VITAL SIGNS AND ORTHOSTATIC VITALS

Basic vital signs are measured while patient is seated at rest and orthostatic blood pressure and heart rate are measured again after 1 minute of standing up. It will be assessed on all participants at the select in-person visits as shown in the SoA.

8.2 SAFETY AND OTHER ASSESSMENTS

8.2.1 PREGNANCY

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Urine pregnancy test will be required as part screening for the eligibility criteria and must be completed on-site on the same day as enrollment and prior to randomization (Day 0). Following a negative pregnancy test result at screening, appropriate contraception must be commenced.

Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by IRBs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

If a participant requiring pregnancy testing cannot visit a local laboratory, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records. If the pregnancy test is positive, the EDP should be reported (Section 8.3.9). Confirm that the participant is adhering to the contraception method(s) required in the protocol

8.2.2 LABORATORY TESTS

Screening laboratory tests including hematology (completely blood count) and serum chemistries (complete metabolic panel) will be required to ensure eligibility is met. This data may be obtained from participant medical records if available within the preceding 6 months or since index COVID-19 infection data, whichever is shorter time-frame, assuming no major interval medical events have occurred since those results.

Hematology and serum chemistries will be repeated immediately post-treatment (Day 15) for safety monitoring. Hematology and serum chemistries may also be performed in the future on

retained blood samples as deemed necessary by investigators as relevant to understanding the safety or complications of PASC and/or the study intervention.

8.2.3 VITAL SIGNS

In addition to the orthostatic blood pressure and heart rate measurements described above under efficacy assessments, additional vital signs such as temperature and pulse oximetry will also be collected during each in-person visit.

8.2.4 ACUTE COVID-19 REINFECTIONS

Rapid COVID-19 antigen testing will be required as part screening for the eligibility criteria and must be completed on-site on the same day as enrollment and prior to randomization (Day 0). If patient is positive and, therefore, does not meet eligibility criteria at that time, they may be retested after 30 days later to reassess eligibility.

Each participant will also be provided to take home rapid COVID-19 antigen tests and instructed to self-test if they develop *new* symptoms consistent with acute COVID-19 re-infection (e.g., fever, cough, dyspnea, rhinorrhea, sore throat, headache, loss of smell or taste, body aches). If the rapid antigen test is positive or as clinically determined by the investigator, the participant will be asked to present for an unscheduled visit for assessments as detailed in SoA. If the antigen test is negative, the participant will perform a second home test 48 hours later to confirm that it remains negative. If the second test is positive, the patient will be asked to present for an unscheduled visit. SARS-CoV-2 reinfection will be recorded as an event of special interest (ESI) in the CRF as discussed in Section 8.3.8.

If the participant is low-risk for progression to severe acute COVID-19 and, as per standard of care (SoC), would not qualify for currently available acute COVID-19 treatments, then we will recommend that they continue in the study.

If the patient is high risk for progression to severe acute COVID-19 and, as per SoC, would qualify for currently available acute COVID-19 treatments, then the following actions will be taken depending on the timing within the study:

- If the participant is reinfected within the 15-day treatment period or within 5 days after the last dose, he/she will be offered unblinding and to seek SoC options for acute COVID-19 treatment.
- If the participant is reinfected during the follow-up period >5 days after the last study intervention dose, then we will provide him/her a 5-day course of Paxlovid as per SoC and continue their follow-up in the study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

AE Definition

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

Any abnormal laboratory test results (e.g., hematology, clinical chemistry, etc.) or other safety assessments (e.g., vital sign measurements, etc.), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:

- *Is associated with accompanying symptoms.*
- *Requires additional diagnostic testing or medical/surgical intervention.*
- *Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.*

Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.

New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.3.2 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 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, or 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.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline does not meet the definition of an SAE. Hospitalization is defined as a stay in the hospital exceeding 24 hours.

An unexpected AE is defined as any AE, the specificity or severity of which is not consistent with the package insert.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

An adverse event (AE) severity grading scale, based on toxicity grading scales developed by the NIH Divisions of AIDS (DAIDS) Toxicity Tables, will be used to grade severity of all symptoms, physical exam findings, and laboratory results (Appendix 3). For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician 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:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Study investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. The Investigator's Brochure will serve as the SRSD for this trial.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) 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.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation. Adverse event monitoring will occur during the period when study drugs are given and through until the end of the study duration (15 weeks). Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form (Pfizer ISR/CRC Interventional SAE Report form).

8.3.5 ADVERSE EVENT REPORTING

At each scheduled and unscheduled visit to the clinic, study clinicians will assess patients according to a standardized case record form. A severity grading scale, based on toxicity grading scales developed by the NIH Divisions of AIDS (DAIDS) Toxicity Tables, will be used to grade severity of all symptoms, physical exam findings, and laboratory results (Appendix 3). All participants, regardless of treatment arm, will be assessed using the same standardized case

record form. Adverse event monitoring will occur during the period when study drugs are given and through until the end of the study duration (15 weeks).

Data will be captured on the incidence of all adverse events as defined in Section 8.3.1, regardless of severity. Adverse events identified and graded as severe or life threatening and felt to be possibly, probably or definitely related to study drugs will be reported to regulatory authorities as per Table 1 below. In addition, an adverse event form will be completed for all captured adverse events in the CRF, regardless of severity and expectedness. The following information will be recorded for all adverse experiences that are reported:

1) Description of event
2) Date of event onset
3) Date event reported
4) Maximum severity of the event
5) Maximum suspected relationship of the event to study drugs (either SP or DP)
6) Whether the event is a serious adverse event
7) Initials of the person reporting the event
8) Outcome
9) Date event resolved

Guidelines for reporting of adverse events provided by the Stanford Institutional Review Board and the Food and Drug Administration (FDA) in the U.S. will be followed as summarized in Table 1 below.

Table 1. Guidelines for reporting adverse events

Institution	Type of Adverse Events	When to Report
Stanford IRB	Adverse event that Stanford PI determines: • changes the study risks or benefits, OR necessitates modification to the IRB-approved consent document(s) and/or the IRB-approved application/protocol	• Within 10 working days of PI's awareness • Unexpected deaths or life-threatening experiences related to the research must be reported to the IRB within 5 working days from PI learning of event
FDA	• Definitely, Probably or Possibly related **AND BOTH** Serious* AND Unexpected±	• For fatal or life-threatening events, by telephone or fax within 7 calendar days of first awareness • All other reportable events within 15 calendar days of first awareness

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE will be recorded on the CRF and the SAE also reported to Pfizer safety using the CT SAE Report Form (Pfizer ISR/CRC Interventional SAE Report form).

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately record any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. All serious adverse events (SAEs) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable.

The study 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.

Any SAE, whether or not considered study intervention related, will also be reported to Pfizer Safety on the CT SAE Report Form (Pfizer ISR/CRC Interventional SAE Report form) immediately upon awareness and within 24 hours. Follow-up on SAEs may also be requested by Pfizer Safety. Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form (Pfizer ISR/CRC Interventional SAE Report form).

Overdose is reportable to Pfizer Safety **only when associated with an SAE.** Any dose of nirmatrelvir greater than 900 mg or ritonavir greater than 300 mg within a 24-hour period will be considered an overdose.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The study clinician will review clinical and laboratory data at each scheduled visit and inform participants about SAEs within 24 hours.

8.3.8 EVENTS OF SPECIAL INTEREST

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

An ESI relevant to this protocol is acute re-infection with SARS-CoV-2. If patient shows symptoms that may indicate COVID-19, an AE will be reported on CRF based on the symptoms. Home antigen tests performed as described in Section 8.2.4 "Acute COVID-19 Reinfections". If COVID-19 reinfection is confirmed by rapid antigen testing, the event will be reported as "COVID-19 reinfection" with start date of symptoms onset (and remove symptoms AEs if entered). If COVID-19 testing is negative, the AE will be updated with a syndromic diagnosis (e.g., upper respiratory infection, gastroenteritis, etc.) after monitoring symptoms.

Drug Induced Liver Injury may also be considered an ESI. Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
- Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).
- Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.3.9 REPORTING OF EXPOSURES (ENVIRONMENTAL, PREGNANCY, OCCUPATIONAL)

8.3.9.1 ENVIRONMENTAL EXPOSURE

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.9.2 EXPOSURE DURING PREGNANCY

Exposure during pregnancy (EDP) occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental EDP:
- A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion.
- A male family member or healthcare provider who has been exposed to the study intervention by ingestion then exposes his female partner prior to or around the time of conception.

EDPs will be recorded and reported on the CT SAE form (Pfizer ISR/CRC Interventional SAE Report form) and an EDP supplemental form within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred (see below for information related to termination of pregnancy). The initial information recorded should include the anticipated date of delivery. Follow up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and record outcome. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator will follow the procedures for reporting SAEs. Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Further follow up of birth outcomes will be handled on a case-by-case basis (e.g., follow up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.9.3 EXPOSURE DURING BREASTFEEDING

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion.

The investigators will report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form (Pfizer ISR/CRC Interventional SAE Report form). When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.
An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.9.4 OCCUPATIONAL EXPOSURE

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form (Pfizer ISR/CRC Interventional SAE Report form), regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form must be maintained in the investigator site file.

8.3.10 MEDICATION ERRORS

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;

- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use;
- The administration of study intervention consistent with the medication error descriptions in Section 6.4.

In the event of a medication dosing error, the investigator should be notified by the study team (including Clinical Research Coordinators within 24 hours. Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors will also be reported to Pfizer Safety within 24 hours on a CT SAE Report Form (Pfizer ISR/CRC Interventional SAE Report form) only when associated with an SAE.

8.3.11 LACK OF EFFICACY

The investigators will assess signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); 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.

Unanticipated problems include both serious adverse events and other adverse events if those events suggest that the research places subjects or others at a greater risk of physical or

psychological harm than was previously known or recognized [45 CFR 46.103(d)(5)]; [21 CFR 56.1069(b)(1)].

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project 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;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 5 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 10 working days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB's receipt of the report of the problem from the investigator.

Further details are available from Stanford IRB reporting policy statement (Appendix 4).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Reporting of AEs and SAEs to participants will follow section 8.3.7. Institutional IRB will determine additional requirement for action in follow-up to reporting of UPs, including potential notification and reconsenting of current participants, when such information might be related to their willingness to continue to take part in the study.

8.5 PHARMACOKINETICS

Blood samples of approximately 4 mL, to provide a minimum of 1.5 mL plasma will be collected at day 15 and stored to allow potential future measurement of plasma concentrations of nirmatrelvir. The date and time of each sample and the time of last drug dose taken will be recorded. Samples collected for analyses of nirmatrelvir concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for

metabolite identification and/or evaluation of the bioanalytic method, or for research related to the study intervention and PASC.

8.6 GENETICS

HLA haplotypes will be evaluated in this study.

Retained Research Samples for Genetics: A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs allow.

Retained Research Samples may be used for research related to the study intervention(s) and COVID-19/PASC. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the samples.

See Appendix 4 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in in the laboratory manual.

8.7 BIOMARKERS

Collection of samples for biomarker research is also part of this study.

The following samples for biomarker research are required and will be collected from all participants in this study as specified in the SoA:

- NP/nasal swab will be collected to measure SARS CoV-2 viral load by RT-PCR. NP swab RT-PCR will be performed at the Stanford clinical laboratory with FDA-approved assay. Rapid antigen tests will be performed using commercially available tests that are FDA-authorized
- Residual NP/nasal viral load samples may be used for SARS CoV-2 viral sequencing. Any positive RT/PCR will be further evaluated by viral genome sequencing by Stanford research laboratories.
- Residual NP/nasal viral load samples may be used for SARS CoV-2 infectivity assays and phenotypic analyses.
- 10 mL blood optimized for plasma may be utilized for proteomics and immunologic studies. Anti-SARS-CoV-2 antibody measurements will be performed by Stanford research laboratories which have been at the forefront of developing such assays since the start of the pandemic, and has performed many thousand assays. T cell responses, EBV antibodies, and CMV antibodies will be measured using research-grade assays. CLIA assays for T cells have not yet been developed by any institutions. CLIA-certified CMV and EBV assays can be conducted if research-grade assays demonstrate differences between groups. Autoantibody profiling and cellular analyte measurements will be performed by Stanford research laboratories and Stanford core facilities using research-grade assays

- 40 ml blood optimized for peripheral blood mononuclear cells (PBMCs) may be utilized for characterization of blood cells. T cell assays will be performed using spheromers, a research-grade assay developed in Stanford research laboratories that has pioneered sensitive detection of SARS-CoV-2-specific T-cell responses.
- 2.5 ml blood optimized for RNA isolation may be utilized to analyze transcript profiles of blood cells.
- 5 ml blood will be collected to measure d-dimer levels.
- 15 ml blood will be collected for biobanking for future assays.
- Stool samples will be collected for SARS CoV-2 RT-PCR. RT/PCR will be performed in stool samples using methods developed in Stanford research laboratories. Stool will also be processed and stored for potential future metagenomic shotgun sequencing if a signal is identified in the trial.

8.7.1 SPECIFIED GENE EXPRESSION (RNA) RESEARCH

Specified gene expression (RNA) research is not included in this study.

8.7.2 SPECIFIED PROTEIN RESEARCH

Blood will be collected for plasma biomarkers as specified in the SoA and may be used for proteomics, immunologic studies, as well as markers associated with coagulation, organ or endothelial cell dysfunction. Residuals of all samples may be banked for future research. Storage and shipping instructions will be in accordance with the laboratory manual.

8.7.3 SPECIFIED METABOLOMIC RESEARCH

Specified metabolomic research is not included in this study.

8.7.4 VIRAL LOAD ASSESSMENTS

An NP/nasal swab will be collected per the SoA, and may be analyzed to measure SARS-CoV-2 RNA by RT-PCR. Residual viral load samples may be utilized for viral sequencing to assess for signs of viral evolution and evaluation of potential genetic viral variants (e.g., 3CL gene) or immune responses, SARS CoV-2 infectivity assays, and additional molecular analysis. Residuals of all samples may be banked for future research. Storage and shipping instructions will be in accordance with the laboratory manual.

8.7.5 RETAINED RESEARCH SAMPLES FOR BIOMARKERS

These Retained Research Samples will be collected in this study:

- 10 mL whole blood optimized for serum Prep B2.
- 10 mL blood optimized for plasma may be utilized for proteomics and immunologic studies.
- 40 ml blood optimized for peripheral blood mononuclear cells (PBMCs) may be utilized for characterization of blood cells.

- 2.5 ml blood optimized for RNA isolation may be utilized to analyze transcript profiles of blood cells.
  5 ml blood for d-dimer testing.
  15 ml blood for biobanking for future emerging assays.

Retained Research Samples will be collected as local regulations and IRB allow according to the SoA. Retained Research Samples may be used for research related to the study intervention(s) and COVID-19 or PASC or their associated risks and complications. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples. Additional assays that emerge regarding PASC pathophysiology may be performed.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8 DIGITAL WEARABLE SUBSTUDY

Exploratory sub-study: For participants who opt-in to the exploratory sub-study, the following will be collected from baseline until end of study using the Apple Watch wearable device and the Welch Allyn Bluetooth-enabled blood pressure (BP) monitor with target goal frequencies as able by the participant:

Measure	Mode	Data collection frequency
Apple Watch		
Accelerometer data (physical activity (PA))	Passive	Continuous
Heart rate and resting heart rate	Passive	Continuous
Heart rate variability	Passive	Continuous
Oxygen saturation level	Passive	Continuous or periodic
Time asleep	Passive	Continuous
Time in bed	Passive	Continuous
ECG rhythm	Active	Daily (D0-15), Weekly (D16-W10), Biweekly (W11 – W15) minimum
Welch Allyn BP Monitor		
Blood pressure (BP)	Active	Daily (D0-15), Weekly (D16-W10), Biweekly (W11 – W15) minimum

Target Schedule of data collection:

	Active	Passive
Day 0 – Day 15 (treatment period)	ECG daily, BP daily	PA, O2sat, HR, HRV, sleep
Day 16 – 10 weeks (primary endpoint)	ECG weekly, BP weekly	PA, O2sat, HR, HRV, sleep
Week 11 – 15 weeks	ECG biweekly, BP biweekly	PA, O2sat, HR, HRV, sleep

Passive: No action is required by the patient for the data collection.
Active: Action is required by the patient to collect the data.

- For the ECG rhythm, the participant will need to press a button on their Apple Watch.
- For the blood pressure, the participant will need to take their blood pressure and record the value.

The schedule above shows the minimum target goal data collection schedule. Participants may check and collect their data more frequently if they desire.
Participants may miss periods of data collection and the study team will reach out to participants to troubleshoot any technical issues and encourage resumption to target goal data collection schedule.

Specific data analysis parameters and analytics algorithms will be defined in a detailed analysis plan prior to data unblinding.

9 STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the intention to treat principle. Randomization will be stratified by vaccination status (completed primary series vs not completed) and the number of symptoms at the baseline (2 or 3 symptoms vs >3 symptoms).

9.1 STATISTICAL HYPOTHESES

For the primary endpoint: 6 core symptoms severity at 10 weeks

- H_0 = There is no difference in the symptom severity in *any* of the 6 core symptoms at 10 weeks between Paxlovid and placebo groups.
- H_1 = There is a difference in the symptom severity of at least one of the 6 core symptoms at 10 weeks between Paxlovid and placebo groups

Secondary endpoints include

- Core symptoms severity based on Likert-scale score at 15 days in participants treated with Paxlovid versus placebo
- Proportion of participants reporting relief at 10 weeks of at least one core symptom for 2 weeks. Relief defined as reduction of severity from moderate to none or severe to mild/none, $\geq$ 2-point Likert score change
- Proportion of participants with overall alleviation at 10 weeks in Paxlovid versus placebo group for 2 weeks. Overall alleviation defined as both: (1) any core symptom(s) that are none/mild (Likert 0 or 1) at baseline are none at 10 weeks and (2) any core symptom(s) that are moderate/severe (Likert 2 or 3) at baseline are none/mild at 10 weeks
- Severity of the most bothersome symptom at 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group

- Time to relief of each of the 6 core symptoms. Relief defined as above.
- Change in PROMIS Physical Function SF 4a v2.0 from baseline to 10 weeks
- Change in PROMIS Fatigue SF 7a v1.0 score between baseline and 10 weeks
- Change in PROMIS Dyspnea-Severity SF 5a v1.0 score between baseline and 10 weeks
- Change in PROMIS Cognitive Function Abilities score between baseline and 10 weeks
- Change in orthostatic vitals (difference in seated versus standing blood pressure and heart rate) from baseline and 10 weeks
- Change in 1-minute sit-to-stand test from baseline and 10 weeks
- Patient Global Impression of Severity scale (PGIS) at 15 days, 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group
- Patient Global Impression of Change scale (PGIC) at Day 15, 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group

The null hypothesis is that there is no difference in the corresponding secondary endpoint between Paxlovid and Placebo groups. The alternative hypothesis is that there is a difference in the corresponding secondary endpoint.

9.2 SAMPLE SIZE DETERMINATION

We plan to enroll 200 patients total with 180 patients completing the 10-week follow-up, i.e., a 10% drop off rate. With a planned randomization ratio of 2:1, we expect approximately 120 patients receiving Paxlovid and 60 patients receiving placebo completing the 15 weeks follow-up at the end of the study. The primary outcome is symptom severity for fatigue, brain fog, dyspnea, body aches, CV symptoms, and GI symptoms in Likert-scale (0, 1, 2, and 3) at 10 weeks. For each aforementioned symptom, we plan to use the proportional odds regression model for ordinal outcomes to compare the Likert scale at week 10 (stratified by their baseline level) among patients experiencing the corresponding symptoms at the baseline. The overall comparison will be made based on averaging regression coefficients from comparisons of individual symptoms weighted by the sample size of the regression analysis, i.e. the number of patients experiencing the corresponding symptom at the baseline (55, 56). The power estimation is made based on following simplified assumptions:

(a) for each symptom, the Likert-scale at week 10 is uniformly distributed over 0, 1, 2, and 3 in the placebo group, i.e., the proportions of the patients with a Likert-scale being 0, 1, 2, and 3 are 25%, 25%, 25%, and 25%, respectively, among all patients in the study including patients without the symptom at the baseline.

(b) for each core symptom, the proportions of the patients in the Paxlovid group with a Likert-scale being 0, 1, 2, and 3 are 34.8%, 26.8%, 21.2%, and 17.2%, respectively, among all study patients.

(c) The z-scores of comparing 6 symptoms using all patients are positively correlated with a pair-wise correlation coefficient of 0.25.

Assumptions (a) and (b) satisfy the proportional odds model with a odds ratio of 1.6. Under this assumption, the z-score of individual comparison based on 60 patients in the placebo group and 120 patients in the Paxlovid group follows a normal distribution with mean of 1.66 and unit variance. The final test statistic is equivalent to the simple average of z-scores from analyses for individual symptoms, since the assumed alternatives are identical for all core symptoms. Under assumption (c) the Wald test statistic for the overall comparison follows a normal distribution with a mean of 2.71 and unit variance, providing a power of 77% at the two-sided significance level of 0.05. The proposed test is expected to have a higher power than that of the analysis discussed above for several reasons. First, the regression analysis excluding patients without the core symptom at the baseline is expected to generate a z-score with a greater mean value and a higher power, since the potential dilution effect from patients without the core symptom at the baseline are reduced. Second, the sample size weighting is expected to generate a more efficient combination of test statistics from individual test than equal weighting. Lastly, the stratification by baseline Likert scale will also increase the power of comparing severity of individual symptom and also the power of overall comparison.

The interim analysis is mainly for assessing futility using conditional power and safety and thus does not affect the sample size calculation. For estimating the timing of the interim and final analysis, we project to enroll one patient per day. Therefore, the interim analysis is expected to be conducted approximately 24 weeks after the first patient in, by which, the outcomes at 10-week follow up will be available for approximately 90 patients. Complete data collection for the outcomes through the 15-week follow up is projected to occur approximately 46 weeks after the first patient in.

Since this is a phase II study, the proposed sample size doesn't necessarily guarantee sufficient power for all secondary endpoints.

9.3 POPULATIONS FOR ANALYSES

The intent-to-treat (ITT) population will include all randomized patients. Patients will be analyzed according to their assigned treatment arm. All efficacy analyses will be completed in the ITT population. The per-protocol (PP) population will include all randomized patients who completed follow-up, adhered to study procedures, and did not have acute COVID-19 reinfection during the study. All efficacy analyses also be completed in the PP population as supportive evidence for the primary efficacy analysis.

The safety population will include all patients who received at least one dose of study treatment. Patients will be analyzed according to actual treatment received. All safety analyses will be completed in the safety population.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics (proportions for categorical variables, means, medians, standard deviations and/or interquartile ranges for continuous variables) will be reported for all key patient variables, including baseline and demographic characteristics, use of medications, compliance, and study completion status. Data that are missing on key patient characteristics and the outcome will be fully described, including any patterns of missingness (i.e., any relationships between missingness of a variable and patient characteristics).

A CONSORT diagram displaying the number of patients screened, eligible, and consented along with reasons for ineligibility will be provided. Graphical tools such as histograms, boxplots, and scatterplots will be created to assess quality of data and to display patterns over time.

All tests will be two-sided and performed at the alpha = 0.05 level of significance unless otherwise noted.

Additional details will be described in a statistical analysis plan (SAP).

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is the Likert-scale of 6 core symptoms at week 10 follow-up. In the subgroup of patients having a positive Likert-scale for each core symptom, we will compare the Likert-scale of the same symptom at week 10 stratified by the baseline Likert-scale between patients receiving Paxlovid for 15 days and patients receiving placebo using the stratified proportional odds regression for each core symptom(s). The estimated regression coefficient of the treatment, i.e., log-transformed odds ratio, is obtained, for measuring the treatment benefit of Paxlovid for the corresponding core symptom. The overall comparison will be made based on a weighted average of the regression coefficient for each core symptom weighted by the sample size of the subgroup in which the regression analysis is conducted, i.e., the number of patients having the corresponding symptom at the baseline, i.e., Likert-scale > 0. A permutation test will be used to generate the null distribution accounting for correlations among estimated regression coefficients for different symptoms (55, 56). This test aggregates the statistical evidence of treatment benefit for each core symptoms and is more powerful if the Paxlovid has a moderate beneficial effect in treating most or all six core symptoms.

Note that since the comparison is stratified by the baseline Likert scale, comparing the symptom severity at the week 10 is equivalent to comparing the change in severity from baseline to week 10.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The key secondary endpoints include core symptoms severity at 15 days, severity of most bothersome symptom at 5 weeks, 10 weeks and 15 weeks, , proportion of subjects reporting relief for 2 weeks of at least one core symptom (reduction of severity from moderate to none or severe to mild/none, a 2-point or greater Likert score change) at 5 weeks, 10 weeks and 15 weeks, and time to relief of at least one core symptom without other symptom worsening, and time to relief of the most bothersome symptom. We will use the proportional odds model to compare the severity of most bothersome symptom at follow-up visit stratified by the baseline

Likert-scale. The subgroup analysis will be repeated according to the most bothersome symptom at the baseline. The analysis of covariance will be used to compare the global symptom severity at follow-up visits adjusting for baseline severity. The same analysis will be used to compare the global impression as well. The logistic regression will be used to compare the probability of experiencing relief for at least one core symptoms, the probability of experiencing relief for the most bothersome symptoms, and the probability of experiencing relief for each core symptom adjusting for baseline Likert-scale of core symptoms. For aforementioned secondary endpoints, we will also use mixed effects model for repeated measurements (MMRM) to compare the longitudinal endpoints across 5-weeks, 10 weeks, and 15 weeks follow-up visits at the same time. The MMRM analysis can borrow additional information from subjects not completing all follow-up visits in two group comparisons and also allow comparing the average endpoints across all longitudinal visits. Lastly, we will use discrete time logrank test to compare the time to relief of at least one core symptom without other symptom worsening, and time to relief of the most bothersome symptom. Patients who don't experience any symptom relief will be treated as right censoring observations. There will be no formal adjustment for multiple testing in analyzing the secondary endpoints. The analysis results for all secondary endpoints will be reported regardless of their statistical significance level, allowing post-hoc adjustment of multiple testing and providing a global picture of the treatment benefit of Paxlovid for long covid patients.

9.4.4 SAFETY ANALYSES

The frequency of adverse events and serious adverse events will be tabulated by type and by treatment arm. AEs will be compared by arm using the Chi-squared test or Fisher's exact test, as appropriate, in the safety analysis set.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

The patients' characteristics at baseline will be summarized and compared between two treatment arms to examine the balance achieved via the randomization. The categorical variables will be summarized by frequency and proportion and the continuous variables will be summarized by mean and standard deviation or median and inter-quartile range as appropriate.

9.4.6 PLANNED INTERIM ANALYSES

We will include an interim analysis for safety assessment and futility assessment utilizing conditional power, when 50% of the planned patients' outcomes at week 10 are available. To this end, a mixed effects regression model will be used to include all enrolled subjects who have completed at least one follow up visit at the interim analysis. A subject-specific random intercept will be included to account for within-subject correlations among symptoms severity at different visits. We will calculate the conditional power based on data available at the interim analysis, assuming the underlying treatment effect size is the same as that observed in the interim analysis. If the conditional power at the interim analysis is less than 20%, the trial will be

stopped for futility. Furthermore, the reinfection rate, early drop off rate, and the proportion of participants with SARS-CoV-2 positive PCR/NAAT and/or positive antigen at the study baseline will be summarized and their impact on study power will be examined. The DSMB will evaluate overall safety and characteristics of the patient population including acute reinfections and potentially recommend enrollment adjustments.

For estimating the timing of the interim and final analysis, we project to enroll one patient per day. Therefore, the interim analysis is expected to be conducted approximately 24 weeks after the first patient in, by which, the outcomes at 10-week follow up will be available for approximately 90 patients.

9.4.7 SUB-GROUP ANALYSES

Subgroup analyses will be conducted to assess potential treatment effect modification on the primary and secondary endpoints in following subgroups:

- Race/ethnic groups (non-Hispanic white, Hispanic, other)
- Sex (male vs female),
- Age (< 50 vs ≥ 50),
- Primary vaccination series completion for COVID-19 (complete vs not complete)
- Number of known COVID-19 infection (1 vs > 1),
- Time since index COVID-19 infection (≤ 6 months vs > 6 months),
- Number of core symptoms at baseline (2-3 vs > 3).
- Prior use of any anti-SARS-CoV-2 therapeutic (yes vs no).

The treatment effects across subgroups will be summarized using a forest plot. The appropriate treatment by covariate interaction will be tested for detecting treatment effect heterogeneity.

9.4.8 EXPLORATORY ANALYSES

Analyses for exploratory biological and digital wearable biomarkers data to be described in the SAP.

9.4.9 SUPPLEMENTAL ANALYSES

We will perform additional variations of the secondary endpoint analyses as part of a supplemental SAP that encompass the following:

- Proportion of participants reporting relief of most bothersome symptom at 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group. Relief defined as above.

- Proportion of participants reporting relief for 2 weeks for each of the 6 core symptoms at 5 weeks, 10 weeks, and 15 weeks. Relief defined as above.
- Time to relief for 2 weeks of at least one core symptom without other core symptoms worsening. Relief defined as above.
- Time to relief for 2 weeks of the most bothersome symptom. Relief defined as above.
- Summative core symptoms severity measured by summation of Likert scale score of 6 core symptoms at 5 weeks, 10 weeks, and 15 weeks in Paxlovid versus placebo group

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: informed consent form (Appendix 1).

10.1.1.2 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 Institutional Review Board (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 participant will sign the informed consent document prior to any procedures being done specifically for the study. 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 given to the participants for their records. 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. 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.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, funder, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB), 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 stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests 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 sponsor.

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

Representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company 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 by the reviewing IRB and Institutional policies.

Participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the research staff will be secured

and password protected. At the end of the study, all study databases will be de-identified and archived.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be entered in the REDCap Cloud database by research coordinators. After the study is completed, the de-identified, archived data will be cleaned, frozen, transmitted to and stored at the Stanford Box folder accessible to the Study PIs.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Stanford Clinical and Translational Research Unit (CTRU) Biorepository. These samples could be used to research the causes of PASC, its complications and other conditions for which individuals with PASC are at increased risk, and to improve treatment. The CTRU Biorepository 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 with regard to biosample storage may not be possible after the study is completed.

10.1.5 KEY INVESTIGATORS

	Role	Department	Email Contact
Upinder Singh, MD	Principal Investigator	Medicine	usingh@stanford.edu
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Haley Hedlin, PhD	Biostatistician	Quantitative Sciences Unit	hedlin@stanford.edu
Lu Tian, PhD	Biostatistician	Biomedical Data Science	lutian@stanford.edu

10.1.6 SAFETY OVERSIGHT

A DSMB will be established by the study team in cooperation with the sponsor to assess at intervals the progress of a clinical trial, safety data, and interim futility analysis using conditional power and recommend to the sponsor whether to continue, modify or terminate the trial. The DSMB will operate according to guidelines documented in a DSMB charter. Minutes will be taken to provide a written record of the DSMB meetings, including interim results; these will be available for review when the trial is complete. The DSMB will be a separate entity from the Institutional Review Board (IRB). The independence of the DSMB is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. DSMB members will not participate in the study as investigators and will not have conflicts of interest regarding the study or the investigational product. The composition of the DSMB will include at minimum a DSMB Chair having experience and expertise in clinical trials, a Scientist with expertise in viral infectious diseases, and a Biostatistician with expertise in clinical trials.

The DSMB will meet before the study, during an interim analysis, and at the conclusion of the trial to review progress of the clinical trial and safety data. The DSMB will review the study for progress and safety. The PI will provide information that will allow the DSMB to review and assess the following:

- The research protocol, informed consent documents and plans for data safety and monitoring;
- Periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome;
- Factors external to the study when relevant information, such as scientific or therapeutic developments, may have an impact on the safety of the participants or the ethics of the trial;
- Study performance to make recommendations and assist in the resolution of problems;
- The safety of the study participants;
- The safety and scientific progress of the trial;
- The continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
- The confidentiality of the data and the results of monitoring; and
- Any problems with study conduct, enrollment, sample size and/or data collection.

The first meeting of the DSMB will take place prior to the initiation of the study to discuss the protocol and the Data Safety Monitoring Plan. Meetings of the DSMB shall be held according to the plan outlined above. Meetings shall be closed to the public because discussions may address confidential patient data. Meetings may be convened as conference calls as well as in person. An emergency meeting of the Board may be called at any time should questions of patient safety arise. The DSMB may request the presence of study investigators at such meetings.

The study PI will distribute study information to the DSMB prior to a scheduled meeting. The DSMB may request additions and other modifications to this information on a one-time or continuing basis. This information will consist of two parts: (1) information on study progress such as accrual, baseline characteristics, and other general information on study status and (2)

any confidential data on study outcomes, including safety data. A formal report from the DSMB should be supplied to the PI within 3 days of each meeting. Each report should conclude with a recommendation to continue or to terminate the study. This recommendation should be made by formal majority vote. A recommendation to terminate the study should be transmitted to the PI and IRBs as rapidly as possible, by immediate telephone and fax if sufficiently urgent. In the event of a split vote in favor of continuation, a minority report should be contained within the regular DSMB report. At the conclusion of the DSMB meeting for the interim safety review planned at 50% enrollment, the DSMB chair will convey the DSMB's recommendation to the study PI in order to minimize the amount of time enrollment is paused.

10.1.7 CLINICAL MONITORING

Clinical 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 Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). This study will be subject to internal monitoring and to external monitoring by DSMB and inspection by regulatory agencies.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The study Data Manager will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

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 study CRC 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 Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

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

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 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 will be completed in a neat, legible manner or electronically to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

All subjects will be given a study ID. Symptom questionnaires and CRFs used at clinic visits will be completed by subjects and or study personnel using only study ID. Specimen containers will be labeled by the CRC only with study ID and date, time of collection. Virologic measurements will be provided back to the study team electronically once available, and entered into a REDCap Cloud database by a CRC.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap Cloud, a 21 CFR Part 11-compliant data capture system. 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.

Electronic data including all study databases and supporting electronic documentation will be archived to cloud-based servers on a daily basis. All data will be kept in secured REDCap Cloud and Box servers. Only the research team will have access to the data.

10.1.9.2 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 Harminosation (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 sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study 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 and reported to sponsor. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the Clinical Trials Registration and Results Information Submission rule (FDAAA 801) and will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. Data from this study may be shared with the drug manufacturer Pfizer, Inc. under a research collaborative agreement. In addition, study results will be disseminated to the public and the medical community through presentations at scientific meetings and publishing manuscripts in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

Any 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 and sponsor institution have 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.

10.2 ADDITIONAL CONSIDERATIONS

We will engage a community advisory board (comprised of stakeholders such as patients, advocates, external experts, etc.) for independent feedback and input about the trial as soon as knowledge of this trial is in the public domain.

10.3 ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRC	Clinical Research Coordinator
CRF	Case Report Form
CTRU	Clinical and Translational Research Unit
DDI	Drug Drug Interaction
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
ESI	Event of Special Interest
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-To-Treat
MOP	Manual of Procedures
NHP	Non-Human Primate
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
NIMP	Non-Investigational Medicinal Product
PASC	Post-Acute Sequelae of SARS-CoV-2
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per Protocol
PRO	Patient Reported Outcome
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOC	Standard of Care
SOP	Standard Operating Procedure
SRSD	Single Reference Safety Document
UP	Unanticipated Problem
US	United States
WOCBP	Women of Childbearing Potential

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	Oct 14, 2022	Major changes include: Wearables sub-study removed, added day 7 home stool collection time-point, added Hy's law provision on potential drug-induced liver injury, collapsing day 5 and day 10 survey timepoints into day 7. Minor changes include: added day 15 symptom severity secondary endpoint, added more subgroup analyses, adjusted reporting parameters to manufacturer, removed certain exploratory labs/assays such as cortisol, etc., and adjusted total blood volume for biobanking.	Incorporating additional suggestions from FDA Antiviral Division, IRB, manufacturer, and DSMB to help improve the scientific rigor, quality, safety, and patient experience the study. Substudy removed from this version while pending additional internal regulatory review. Some exploratory assays were removed due to budgetary limitations, but blood volume adjusted to allow for biobanking for emerging assays
1.2	October 25, 2022	Major changes include: switched PCFS instrument to PROMIS Physical Function instrument, included PGIS global impression scale, shifted several secondary endpoints to supplemental SAP given their similarity and slight variation in analysis to others. Minor changes include: symptoms survey query "at its worst" instead of "on average" in last 7 days, added individual items in parantheses after some broad symptoms to clarify, added 2 weeks duration to relief and alleviation endpoints, reduced number of items classified as key secondary endpoints.	Incorporating additional suggestions from FDA DCOA Division regarding the clinical outcomes assessments, in particular patient reported outcomes and clarifications or adjustments in analyses.
1.3	October 31, 2022	Major change includes: re-added exploratory wearables sub-study Minor change: secondary endpoints' list in SAP copy-edited for consistency with rest of document; stool collection schedule updated	Wearables sub-study passed internal regulatory data and privacy review Stool collection schedule updated per FDA as prior and budget
1.4	November 10, 2022	Minor changes: stool collection during unscheduled visit adjusted to at investigator's discretion, removed redundant exclusion criteria #10, adjusted supplements exclusion criteria timeframe to per investigator's discretion given variability in type and	Minor updates and clarifications

		safety profile of supplements, clarified vaccine exclusion criteria timeline for COVID vs other vaccines, updated Pfizer safety reporting form name and clarified redundant reporting text, updated prohibited medications appendix per latest FDA fact sheet, clarified wearables trend over time endpoint, typographical edits.	
1.5	December 5, 2022	Major changes include: Final study visit at 15 weeks instead of 18 weeks, drug-drug interaction appendix removed with reference to latest FDA Fact Sheet instead. Minor changes include: Increased screening period to 14 days from 10, modified unscheduled visit to investigators' discretion, added exclusion criteria for planned study drug use during study outside of FDA authorized indication, modified 3-minute standing orthostatics test to simple sit-stand orthostatics.	Final study duration changed due to patient experience, adherence, and potential confounding events that occur during longer follow-up. Drug-drug interaction appendix is not easily kept up-to-date as referencing the latest FDA Fact Sheet and updated, reliable online interaction checker, and investigator's discretion on drugs with minimal interaction data.
1.6	January 20, 2023	Major changes include: AE definition further clarified in Section 8.3 Minor changes: modified screening lab chemistries, added process for managing difficulty swallowing ritonavir, clarified wearables schedules as target goals and added process for following up with patients who may miss periods of wearable data collection, schema figure stool schedule error fixed, deleted numbers to home antigen kits.	AE capture threshold clarified to capture what is more clinically significant, relevant, and meaningful. Minor updates to chemistries and pill swallowing management done to improve patient experience and participation. Substudy update to clarify data collection. Antigen kit number flexibility for package variations.
1.7	March 27, 2023	Minor changes include: Schedule of Activities footnote added for optional in-person activities for visits #3 and #5 for select participants with significant travel or logistical barriers; inclusion criteria clarification for confirmation of testing either by documentation or self-report (latter not to exceed 15% of enrollment); $250 additional compensation offered for participants traveling in from out of the area	To expand recruitment and promote participant engagement and retention, particularly for those with significant travel or logistical barriers.
1.8	May 5, 2023	Minor changes include: Clarification of the analysis plan for interim analysis including futility assessment and conditional power threshold	Efficacy is understood to represent interim futility analysis, which is to be conducted utilizing Conditional

			Probability with no effect on *alpha*.

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12 APPENDICES

12.1 APPENDIX 1. INFORMED CONSENT

. Are you participating in any other research studies? _____ Yes _____No

CONCISE SUMMARY

We are asking your consent in order to participate in a RESEARCH study.

It is very important to know that your participation is entirely VOLUNTARY.

> **The purpose** is to study whether PAXLOVID can reduce or eliminate Long COVID (a.k.a., PASC) symptoms and whether it causes any side effects. We do not know whether this medication will be effective for PASC.
> **The duration** of your participation in the study would be 15 weeks (**3.5 months**).

If you are eligible to participate, you will be randomly selected to receive **either the drug or placebo at a 2:1 ratio** which means twice as many participants will receive the drug as the placebo.
The test treatment involves taking the **study drug** orally twice a day **for 15 days**.
There are a total of **5 clinic visits** scheduled for in-person, including at enrollment (study entry), then approximately at 15 days, 5 weeks, 10 weeks, and 15 weeks after enrollment. Requirement for in-person activities for Week 5 and Week 15 visits may be discussed with study team for individuals who have significant travel or other logistical barriers to come in person.
You will be asked to do the following:
Symptoms surveys up to weekly throughout the study (online)
Other questionnaires by/at each clinic visit (online or in person)
Blood collection at each clinic visit
Nasopharyngeal (deep nose) swab at each clinic visit
Stool collection at 3 visits and a week into study (kit given for home collection)
Vital signs and a **1-minute sit-stand test** at each clinic visit
Your **medications and supplements** will be reviewed carefully and frequently throughout the study and all changes must be alerted to the study team for your safety.
Optional sub-study: If you have an iPhone, you may be invited to participate in a sub-study to track your digital health data such as physical activity and heart rate from a wearable device (a smartwatch – this will be provided to you if you wish to participate in this sub-study). Participating in this sub-study is optional.
Possible risks may include discomfort from study procedures, side effects from the drug, and unforeseeable consequences as with any research study.
Possible benefits may include taking a *potentially* effective medication for PASC, but we cannot and do not guarantee or promise that you will receive any benefits from this study.
Alternative to the study is to not participate in the study.

PURPOSE OF RESEARCH

You are invited to participate in a research study of PAXLOVID (nirmatrelvir and ritonavir) to treat Long COVID (also called Post-Acute Sequelae of Sars-CoV2 or PASC). The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients at high risk for severe COVID-19 infection. However, PAXLOVID has not been approved by the FDA. The use of PAXLOVID for PASC has not been tested yet and there are some potential risks with taking this drug. We will hope to learn whether 15 days of oral administration of this medicine will decrease or eliminate your Long COVID symptoms and whether it causes any side effects. In addition, if there is a benefit, we will hope to learn the possible reason for this observation. You were selected as a possible participant in this study because you have been diagnosed with Long COVID and have had symptoms lasing for at least 3 months.

If you decide to terminate your participation in this study, you should notify Dr. Upinder Singh and Dr. Linda Geng at 650-723-4045.

This research study is looking for 200 adults diagnosed with Long COVID in the US. Stanford expects to enroll all 200 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

This research study will recruit 200 participants to complete 15 weeks (3.5 months) of follow-up.

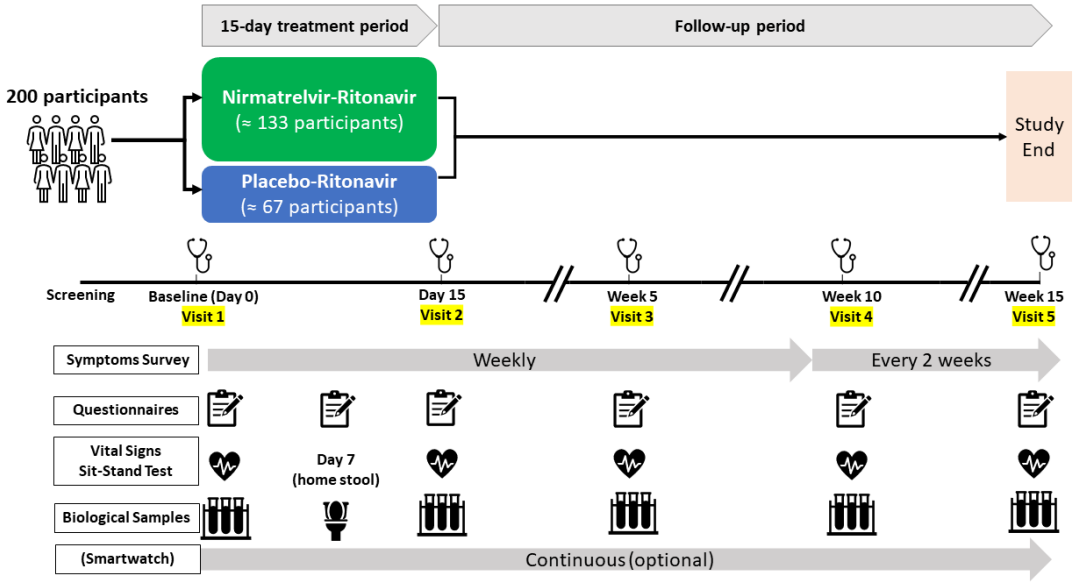
PROCEDURES

This study will assess whether PAXLOVID (nirmatrelvir and ritonavir) can alleviate or resolve your Long COVID symptoms. Nirmatrelvir has activity against the SARS-CoV-2 virus and ritonavir does not have any biological activity against SARS-CoV-2 but is given with nirmatrelvir to increase its level in the body. The PAXLOVID medication is given as 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) with all three tablets taken together by mouth twice daily for 15 days. We will also assess whether this medication and dose causes any side effects.

PAXLOVID, tested in over 4000 healthy people, was highly effective in reducing the risk of severe COVID-19 and death. As a result, the U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of PAXLOVID, which includes the treatment of mild-to-moderate COVID-19 in adults and pediatric patients.

Because we do not know if PAXLOVID will work for Long COVID, participants will be selected at random to receive PAXLOVID or a placebo (inactive) medication. The placebo group will also receive ritonavir which has no activity against SARS-CoV-2, but it is given to match the ritonavir given in the PAXLOVID group. The participants, doctors and staff involved in the study will not know who is receiving the drug or the placebo. The PAXLOVID and placebo groups will be compared after the study has completed to see whether the medication is more effective than the placebo medication. For each participant, there is a 2/3 chance of getting PAXLOVID and a 1/3 chance of getting placebo. So, you will have a two times higher chance of receiving PAXLOVID than a placebo drug.

Study overview



If you choose to participate, you will be asked to do the following.

• **Before the first (enrollment) visit:** The study team will review with you ALL of your prescribed and over-the-counter medications and supplements. **It is very important for your safety that the study team is informed of everything you are taking.**

May request that you hold certain supplements and herbs before enrollment and after this period as determined necessary by investigators, unless medically indicated (e.g., for nutrient deficiency) and determined to be safe by investigators.

Supplements and herbs include a wide range of products including vitamins, minerals, probiotics, botanicals, amino acids, enzymes, tinctures, etc.

Request that you and your doctor(s) do not plan to add new or significantly changed doses of immune-related medications from 30 days prior to enrollment until 10 weeks after enrollment.

Immune-related medications include immunosuppressants and immunomodulators such as steroids (e.g., prednisone), biologics (e.g., infliximab), azathioprine, low-dose naltrexone, etc.

You should NOT stop any medications that are medically necessary for your health conditions. If you are currently taking any medically necessary medications that interact with the study drug, you may not be able to participate in the study. If later during the study you need to start taking any medically necessary medications that interact with the study drug, you may be asked to stop the study treatment.

• At the first (enrollment) visit:

The study team will

Review the informed consent with you, answer any questions you may have, and confirm that you fully understand it.

Assess eligibility including asking about your Long-Covid symptoms and reviewing your medical records to ensure that you are eligible for the study

Assess your current medications, including prescribed and over the counter medications, supplement, and herbs to ensure that you can safely participate in the study.

Give you an ID number that we ask you to save for future use.

Collect urine for a pregnancy test if you a woman of reproductive age and have the potential to have children. A negative test during this study visit is required before receiving the study drug even if you already know you are not pregnant. During follow-up phone calls and visits, the study doctor or staff may ask and talk to you about any possible pregnancy.

Perform a rapid antigen COVID-19 test

Collect 80 ml (about five and a half tablespoons) of your blood by venipuncture. This blood will be used for biological tests. Any remaining blood will be stored for future studies in the Biobank facility at Stanford University.

Swab your nasopharynx (deep inside your nose) for SARS-CoV2 and potentially other viruses

Provide you a kit to collect a stool sample at home which will be mailed back to us

Ask that you complete questionnaires including about your symptoms and overall health

Check your vital signs (including blood pressure and heart rate lying down and standing up, temperature, and blood oxygen saturation level)

Perform a physical function test (asking you to sit and stand from a chair as many times as you are able in 1 minute)

The study team will provide you a Medication Alert bracelet and wallet card to use while you are taking the study drug.

If you agree to participate in the Digital Wearable portion of the study, please see additional details on page 18.

If you are eligible for the trial, you will be randomly assigned to either receive PAXLOVID or placebo. You will be instructed on how to take the pills and keep track of the number of medications. If you have any questions or concerns about taking your medications or missed doses, please contact the study team at **TreatCOVID@stanford.edu** or call **650-308-6788**.

• **Online symptoms questionnaire:**

At home, after the first visit and periodically throughout the trial, you will complete an online questionnaire accessible by computer or cell phone. On this questionnaire, you will be asked to respond to questions about symptoms of Long COVID or of medication effects that you may experience.

During the first 10 weeks, the questionnaire will weekly.

After 10 weeks, the questionnaire will occur every 2 weeks through the end of the trial at 15 weeks.

• **Home stool collection:**

At home, a week after the first visit, you will be asked to collect a sample of your stool:

7 (+/- 2 days) after enrollment (kit provided for you to collect stool sample at home and mail back)

• **Returning visits to the clinic for assessments:**

There are 5 scheduled in-person visits for the study: enrollment, and 15 days, 5 weeks, 10 weeks, and 15 weeks after starting therapy. Additional visits may be required per the discretion of the investigator (if you develop any symptoms consistent with acute COVID reinfection, have a positive SARS-CoV-2 test, or have other new concerning symptoms, etc.) for clinical assessment, nasopharyngeal swab, and blood sample collection. *Requirement for in-person activities for Week 5 and Week 15 visits may be discussed with study team for individuals who have significant travel or other logistical barriers to come in person.

We will provide you with a calendar and appointments for these visits. All visits will be during Mon-Friday and no visits will be on the weekend. These return visits will occur at:

15 days (+/- 2 days) after enrollment

5 weeks* (+/- 7 days) after enrollment

10 weeks (+/- 7 days) after enrollment

15 weeks* (+/- 14 days) after enrollment

At each return in-person clinic visit, the following will be performed:

Blood collection of 80 ml (about five and a half tablespoons) by venipuncture. These samples will be used to look for medication effects and to store for future work on immune responses and viral biology in the Biobanking facility at Stanford University.

Nasopharyngeal (deep nose) swab for SARS-CoV2 (the virus that causes COVID-19) and potentially other viruses

Stool sample collection around days 15 and week 10 (kit provided for you to collect at home and mail back)

Questionnaires including symptoms of Long COVID and overall health

Vital signs including blood pressure and heart rate sitting down and standing up, temperature, and blood oxygen saturation level

Physical function test (asking you to sit and stand from a chair as many times as you are able in 1 minute)

You will be tested for communicable diseases (COVID-19) as part of this research study. If your test results are positive, the results will be reported to health authorities as required by law.

We will also ask you to return any unused medication to us so it can be properly disposed.

At the end of the study, if you are also participating in the Digital Wearable sub-study, we will ask you to return the Apple Watch and blood pressure monitor. See page 18 regarding details of the Digital Wearable sub-study.

Your specimens may be sent outside of Stanford for analysis. This research might include whole genome sequencing of specimens. Any of your samples that are used in the study may result in new products, tests, or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University, and/or others. However, donors of specimens do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests, or discoveries.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breastfeeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breastfeeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation for at least one months after receiving PAXLOVID or Placebo. You must accept the risk that pregnancy could still result despite the responsible use of a reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method or if you become pregnant. Due to safety reasons, pregnancy may result in your being withdrawn from the study.

If you are a man participating in this study and your partner is able to become pregnant, you and your partner must use adequate contraception while you are participating in the study and for at least one month. Your doctor will discuss with you

what methods of birth control are considered adequate. You should inform your study doctor if your partner becomes pregnant.

Future Use of Private Information and/or Specimens

Research using private information and/or specimens is an important way to try to understand human disease. You are being given this information because the investigators want to save private information and/or specimens for future research.

Your specimens will be stored with a study ID. After the study is complete, all personal identifiers linked to the study ID will be destroyed. Because your specimens will not be linked to your name after they are stored, you cannot withdraw your consent to the use of the specimens after they are taken.

Identifiers might be removed from identifiable private information and/or identifiable specimens, and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Genetic Testing and Future Research

As part of the analysis on your specimens, the investigators may do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

The process of determining all or nearly all of your DNA sequence is called whole genome sequencing. It is different from genetic testing that does not involve whole genome sequencing because it provides a much more detailed snapshot of your genome. This research might include whole genome sequencing.

The results of the study of your data and/or specimens from this project will be used for research purposes only, and you will not be told the results of the tests.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

Follow the instructions of the Protocol Director and study staff.
Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff.
Complete the smart phone/computer questionnaire as requested by study staff.
Tell the Protocol Director or research study staff about any side effects, medication changes, illness, doctor visits, or hospitalizations that you may have.
Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
Ask questions as you think of them.

Tell the Protocol Director or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Dr. Upinder Singh and Dr. Linda Geng at 650-723-4045.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

Failure to follow the instructions of the Protocol Director and study staff.
The Protocol Director decides that continuing your participation could be harmful to you.
Pregnancy
You need treatment not allowed in the study.
The study is cancelled.
Other administrative reasons.
Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

You will be asked to come to our research clinic on five (5) occasions. (Additional office visits may be scheduled up to discretion of the investigator team as necessary for safety or other medically related events).

We will collect blood samples on up to five occasions. Blood draws can cause discomfort, bruising and very, very rarely, infection at the needle site. Some people also feel faint. We will try to minimize these risks by having well-trained blood drawing staff draw your blood.
We will collect nasopharyngeal swabs on up to five occasions. Nasopharyngeal swabs can cause discomfort. We will try to minimize this risk by having well-trained staff using proper techniques perform the swabs.
2/3 of subjects will receive nirmatrelvir and 1/3 will receive placebo (inactive) drug. All subjects will receive ritonavir. Known potential risks associated with nirmatrelvir include vomiting and headache. Known potential risks associated with ritonavir include gastrointestinal disturbances (including diarrhea, nausea, vomiting and abdominal pain), Neurological disturbances (eg, tingling sensation, altered taste, and dizziness), Rash, and Fatigue. Other less common side effects may include diarrhea, high blood pressure, muscle aches, abdominal pain, nausea, malaise. Other risks or side effects may include: Risk of Serious Adverse Reactions Due to Drug Interactions, Allergic Reactions/ Hypersensitivity, Hepatotoxicity, and Risk of HIV-1 Resistance Development. For individuals with undiagnosed or uncontrolled HIV, administration of this drug could lead to resistance of HIV to protease inhibitors.
We do not know if this medication will be effective for Long-Covid. All subjects, whether receiving treatment or the standard-of-care, may have worsening of symptoms. Because we will be monitoring your symptoms, and because you can contact us with any concerns, you will have rapid access to further medical care
Any study may have unforeseeable consequences to subjects. By carefully monitoring the progress of this study, we will be able to respond to these problems in a timely manner.

POTENTIAL BENEFITS

The main purpose of this study is research. Because of this, you may or may not get any health benefit from being in the study. PAXLOVID may reduce the duration and severity of symptoms related to Long COVID.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

The alternative to participating is not to participate.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law**.** However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to learn whether 15 days of oral administration of PAXLOVID will reduce or eliminate your Long COVID symptoms and whether it causes any side effects. The results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

The purpose of this study is to see if the drug, PAXLOVID can reduce or eliminate the symptoms of Long COVID. Health information you provide will determine whether you are eligible to participate in the study and whether the medication has affected your symptoms in any way. Blood, stool, and nasopharyngeal samples you provide will help determine whether the medication can change possible biomarkers of persistent SARS-CoV-2.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any

research-related treatment. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Upinder Singh at Lane Building, Room L134, 300 Pasteur Dr., Stanford University, Stanford CA. 94305-5107.

What Personal Information Will Be Obtained, Used or Disclosed?

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, name and initials, address, email, phone number(s), date of birth, age, sex, race, ethnicity, medical record number, health history and information related to COVID-19 disease and symptoms, questionnaires, symptoms that might relate to medication side effects, vital signs including temperature and blood oxygen saturation levels, laboratory and radioimaging investigation reports, pregnancy test and tests of viral shedding of COVID-19 and other viruses, medication received including study drug, and phone call records.

The Digital Wearables sub-study will also have the AiCare app collect the following data: physical activity, heart rate, heart rate variability, BP, step count and ECG via the smartwatch.

Who May Use or Disclose the Information?

The following parties are authorized to use and/or disclose your health information in connection with this research study:

The Protocol Director, Dr. Upinder Singh
The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
Research Staff

Who May Receive or Use the Information?

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

The Office for Human Research Protections in the U.S. Department of Health and Human Services
Pfizer, the manufacturer of PAXLOVID
AiCare, Inc.
The Food and Drug Administration
The study's Institutional Data Monitoring Committee at Stanford

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?

Your authorization for the use and/or disclosure of your health information will end on May 1, 2050 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____

Signature of Adult Participant Date

_____

Print Name of Adult Participant

FINANCIAL CONSIDERATIONS

Payment/ Reimbursement

You will be paid [redacted] for each visit to the clinical site to compensate you for travel expenses and inconvenience. If you live greater than 2-hour driving distance away (about 100 miles) from the clinical site, you will be paid an additional [redacted] for each completed in-person visit to off-set additional travel expenses. You will be paid [redacted] for completing the Day 7 home activities. Preferred method of payment is gift card after the completion of each study visit.

Payments may only be made to U.S. citizens, legal non-citizens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

Costs

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance.

Sponsor

Pfizer will be providing the medications, PAXLOVID and Placebo, for this study. Pfizer is providing funding for the conduct of this study.

Consultative or Financial Relationships

None of the protocol directors and study investigators have any consultative or financial relationships with Pfizer, Inc.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical

treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

Due to the coronavirus public health emergency, the federal government has issued a Declaration that may limit your right to sue if you are injured or harmed while participating in this COVID-19 study. If the Declaration applies, it limits your right to sue researchers, healthcare providers, any study sponsor, manufacturer, distributor or any other official involved with the study. However, the federal government has a program that may provide compensation to you or your family if you experience serious physical injuries or death. To find out more about this "Countermeasures Injury Compensation Program" please go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

STOP-PASC Digital Wearable Sub-Study

This is an optional sub-study within the main STOP-PASC trial. You may still participate in the main STOP-PASC trial regardless of whether or not you decide to participate in this digital wearable sub-study.

Purpose: Digital wearable devices such as smartwatches are electronic devices that people wear to track personal health data, such as monitoring their heart rate and how many steps they have taken in a day. The purpose of this sub-study is to track changes in participant's health condition over time and better understand the impact of treatments using these quantitative measures such as heart rate and physical activity.

Eligibility: To enroll in this digital wearable study, you must meet all of the following criteria:

consent to the main STOP-PASC trial
currently own an Apple iPhone 8 or newer (or iOS 16) with a data plan and is the sole user of that iPhone
agree to download and maintain the free third-party AiCare and Welch Allyn apps, as needed, onto the iPhone for the duration of the study
able to read and speak English
are able and willing to comply with all study procedures
do NOT have known hypersensitive skin, allergies to wristbands of Apple Watches or wristbands of similar products, or severe allergy to nickel or metal jewelry

Devices provided: We will loan these devices to you to take home for the duration of the study:

one (1) smartwatch: Apple Watch Series 7 or newer
one (1) blood pressure (BP) monitor: Welch Allyn 1500 Series with Bluetooth

You may use your own device if you already own these models or have an equivalent or newer model that is compatible with our system.

Procedures:

Wearing the smartwatch: You will be asked to wear, or continue to wear, the smartwatch (Apple Watch) on your wrist, 24/7 (around the clock) as possible for the duration of the study which is 15 weeks (3.5 months) except when charging and during

water activities if desired. The smartwatch is water resistant and can be worn in shallow water activities such as showering, bathing, or swimming in the pool or ocean, but can be removed temporarily during those activities if you prefer. You will be asked to charge the smartwatch for 1 hour daily.

Installing the apps: The clinical study coordinator will assist you to download and install the free AiCare and Welch Allyn apps on your smartphone. The smartwatch will allow Bluetooth signaling to be picked up by the AiCare app on your smartphone. You may be asked to review and agree to any Privacy Policies, Terms of Service, or End User Licensing Agreements when downloading the apps onto your phone. This is separate from this consent form. You should review these terms carefully prior to agreeing to them. You do not have to agree to these agreements/terms. If you do not, you cannot participate in the sub-study but can still participate in the main study.

Data collection: Your physical activity, heart rate, heart-rate variability, and blood oxygen saturation level will be collected continuously for the duration of the study. Other data from the smartwatch such as sleep patterns may also be collected. These are passive data collection which means no action is required from you to collect this data. Your smartwatch data is collected securely by the AiCare phone app and AiCare website, and it can also be viewed by the clinical trial study coordinator. AiCare will securely transmit your smartwatch data to the Stanford study team for further research analysis.

You will be asked to check your ECG rhythm (press of a button on smartwatch) and also check your blood pressure (BP) with the home BP monitoring kit at this following schedule at a minimum:

Day 0 – ~Day 15 (during the study drug administration period): daily the same time each morning

~Day 16 – Week 10: every week

Week 11 – 15 weeks (end of study): every two weeks

You are welcome to check more frequently than the above schedule if desired but this is not required. Blood pressure checks should be performed according to manufacturer's instructions to ensure accurate measurements.

Monitoring: Please note that your smartwatch data will not be continuously monitored in real-time by a medical professional. If you have any concerns or questions about your health-related smartwatch values, please call your doctor and seek medical care. The clinical research coordinator may contact you via email and/or phone if there are significant changes in the data recordings based on automated data completeness parameters set by AiCare. If there is no data transmitted for 24 hours, the study coordinator will contact you to answer simple questions and clarify proper use of the smartwatch. If the research team is unable to reach you, the back-up contact person will be contacted.

Return of devices: After completing the study, you will return any loaned devices (smartwatch and/or blood pressure monitor) as directed by the study coordinator.

Risks and benefits:

There is a small risk of irritation or allergic reaction from wearing the smartwatch. These are usually well tolerated and worn by millions of people. A prior clinical trial did not demonstrate any significant adverse skin effect to anyone. Please let us know if there is any irritation to your wrist or any skin changes.

The sub-study may help with detecting changes in PASC symptom severity, overall health status, and potential responses to treatment.

We cannot and do not guarantee or promise that you will receive any benefits from this sub-study.

Participant's rights: Your participation in this sub-study is voluntary and you have the right to withdraw your consent or discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. You may still continue to participate in the main STOP-PASC trial if you withdraw from the Digital Wearable sub-study. See pages 10 and 22 in the main study for additional participant's rights.

Confidentiality: The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research sub-study is to explore the correlation between the digital biometric data collected via the AiCare platform and PASC symptoms; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Identifiers might be removed from identifiable private information and/or identifiable specimens and, after such removal, the information and/or specimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

Conflict of interest:

The Protocol Directors and the rest of the investigators have no financial interest in AiCare.

☐ _____ (initials and date) Yes, I wish to participate in the STOP-PASC Digital Wearable Sub-Study.

☐ _____ (initials and date) No, I do not wish to participate in the STOP-PASC Digital Wearable Sub-Study.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Directors, Dr. Upinder Singh, or Dr. Linda Geng. You may contact her now or later at 650-723-4045.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, Upinder Singh, or page Dr. Linda Geng, at 650-723-4045.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact the study team at [redacted].

Alternate Contact: If you cannot reach the Protocol Directors, please contact Dr. Hector Bonilla at [redacted].

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

be informed of the nature and purpose of the experiment;
be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
be given a description of any attendant discomforts and risks reasonably to be expected;
be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
be given an opportunity to ask questions concerning the experiment or the procedures involved;
be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
be given a copy of the signed and dated consent form; and
be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you?
____ Yes ____ No

Signing your name below means you agree to be in the STOP-PASC study and that you will receive a copy of this signed and dated consent form.

_____ _____

Signature of Adult Participant Date

_____ _____

Print Name of Adult Participant Time of Consent

Legally Authorized Representative

The legally authorized representative should sign if the participant is unable to sign for themselves. The relationship between the study participant and the representative should be stated.

_____ _____

Signature of Legally Authorized Representative (LAR) Date

(e.g., parent, guardian or conservator)

_____

Print Name of LAR

_____

LAR's Authority to Act for Participant

(e.g., parent, guardian or conservator)

Person Obtaining Consent

_____ _____

Signature of Person Obtaining Consent Date

_____

Print Name of Person Obtaining Consent

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____

Signature of Witness Date

_____

Print Name of Witness

(e.g., staff, translator/interpreter, family member)

Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.

The English consent form (referred to as the "Summary Form" in the regulations):

Must be signed by the witness AND the Person Obtaining Consent (POC).

The non-English speaking participant/LAR does not sign the English consent.

The non-English speaking participant/LAR should not sign the HIPAA participant line

If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.

12.2 APPENDIX 2. CONTRACEPTIVE AND BARRIER GUIDANCE

12.2.1 MALE PARTICIPANT REPRODUCTIVE INCLUSION CRITERIA

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use contraception/barrier as detailed below:
- Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in Section 12.2.4).

12.2.2 FEMALE PARTICIPANT REPRODUCTIVE INCLUSION CRITERIA

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 12.2.3).

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), as described below, during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). If a highly effective method that is user dependent is chosen, a second effective method of contraception, as described below, must also be used. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are coadministered, a barrier method or other nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

12.2.3 WOMAN OF CHILDBEARING POTENTIAL

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

2. For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 50 years of age and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.2.4 CONTRACEPTION METHODS

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.

2. Intrauterine device.

3. Intrauterine hormone releasing system.

4. Bilateral tubal occlusion (eg, bilateral tubal ligation).

5. Vasectomized partner:
    - A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal.

7. Progestogen only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.

8. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

In addition, one of the following effective barrier methods must also be used when option 6 or 7 are chosen above:

- Male or female condom with or without spermicide;

- Cervical cap, diaphragm, or sponge with spermicide;

- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

Because ritonavir may reduce the effect of estradiol-containing contraceptives when agents are co-administered, a barrier method or other nonhormonal method of contraception must also be used if the participant is using estradiol-containing contraceptives.

12.3 APPENDIX 3. DAIDS TOXICITY TABLE CORRECTED V2.1

Division of AIDS Table for Grading the Severity of ADULT AND PEDIATRIC Adverse Events Corrected Version 2.1, July 2017

The Division of AIDS (DAIDS) oversees more than 300 clinical trials domestically and internationally, which evaluate the safety and efficacy of therapeutic products, vaccines, and other preventive modalities. Adverse event (AE) data collected during these clinical trials form the basis for subsequent safety and efficacy analyses of pharmaceutical products and medical devices. Incorrect and inconsistent AE severity grading can lead to inaccurate data analyses and interpretation, which in turn can impact the safety and well-being of clinical trial participants and future patients using pharmaceutical products.

Over the years, DAIDS scientific knowledge and experience have expanded, necessitating revisions of the DAIDS grading table which serves as a guide for assessing the severity of AEs (including clinical and laboratory abnormalities) in participants enrolled in DAIDS-sponsored and -supported clinical trials. The *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* updates and replaces version 2.1 (March 2017).

Glossary/Definitions of terms used in tables:

AE	Adverse event; Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
AV	Atrioventricular
Basic Self-care Functions	Adult Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding.
	Young Children

	Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
BMI z-score	Body mass index z- score; A body reference norm. Specifically, the number of standard deviations a participant's BMI differs from the average BMI for their age, sex, and ethnicity.
BMD t-score	Bone mineral density t-score; The number of standard deviations above or below the mean bone mineral density of a healthy 30 year old adult of the same sex and ethnicity as the participant.
BMD z-score	Bone mineral density z-score; The number of standard deviations a participant's BMD differs from the average BMD for their age, sex, and ethnicity.
BPAP	Bilevel positive airway pressure; A mode used during noninvasive positive pressure ventilation.
Chemical Pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
CNS	Central nervous system
CPAP	Continuous positive airway pressure
DAERS	DAIDS Adverse Experience Reporting System; An internet-based system developed for clinical research sites to report Expedited Adverse Events (EAEs) to DAIDS. It facilitates timely EAE report submission and serves as a centralized location for accessing and processing EAE information for reporting purposes.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
Hospitalization	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labor and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
INR	International normalized ratio

Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
IV	Intravenous
IVIG	Intravenous immune globulin
LDL	Low density lipoprotein
LLN	Lower limit of normal
Life-threatening AE	Any adverse event that places the participant, in the view of the investigator, at immediate risk of death from the reaction when it occurred (i.e., it does not include a reaction that would have caused death if it had occurred in a more severe form).
NA	Not applicable
Participant ID	The identification number assigned to a study participant which is used to track study-related documentation, including any reported AEs.
PR Interval	The interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles.
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc Interval	The measure of time between the onset of ventricular depolarization and completion of ventricular repolarization corrected for ventricular rate.
RBC	Red blood cell
SI	Standard international unit
ULN	Upper limit of normal
Usual Social & Functional Activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby.

	Young Children Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.
WBC	White blood cell
WHO	World Health Organization
WNL	Within normal limits

Instructions for use

The *Division of AIDS* (*DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1* consists of parameters, or AEs, with severity grading guidance that are to be used in DAIDS clinical trials for safety data reporting to maintain accuracy and consistency in the evaluation of AEs. The term "severe" is not the same as the term "serious" in classifying AEs. The severity of a specific event describes its intensity, and it is the intensity which is graded. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition.

Clinical sites are encouraged to report parameters in the DAIDS grading table as they are written to maintain data consistency across clinical trials. However, since some parameters can be reported with more specificity, clinical sites are encouraged to report parameters that convey additional clinical information. For example, diarrhea could be reported as neonatal diarrhea; seizures, as febrile seizures; and pain, as jaw pain.

General Considerations

The DAIDS grading table provides an AE severity grading scale ranging from grades 1 to 5 with descriptions for each AE based on the following general guidelines:

Grade 1 indicates a mild event

Grade 2 indicates a moderate event

Grade 3 indicates a severe event

Grade 4 indicates a potentially life-threatening event

Grade 5 indicates death (Note: This grade is not specifically listed on each page of the grading table).

Determining Severity Grade for Parameters "Between Grades"

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE. If a laboratory value that is graded as a multiple of the ULN or LLN falls between two grades, select the higher of the two grades for the AE. For example, Grade 1 is 2.5 x ULN and Grade 2 is 2.6 x ULN for a parameter. If the lab value is 2.53 x ULN (which is between the two grades), the severity of this AE would be Grade 2, the higher of the two grades.

Values Below Grade 1

Any laboratory value that is between either the LLN or ULN and Grade 1 should not be graded.

Laboratory Values

General. An asymptomatic, abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited timeframe unless it meets protocol-specific reporting requirements. Sites should refer to the applicable network standards for reporting abnormal laboratory findings on the clinical case report forms.

Values below Grade 1. Any laboratory value that is between the ULN and grade 1 (for high values) or the LLN and grade 1 (for low values) should not be graded or reported as an AE. Sites should consult the *Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0* and their protocol when making an assessment of the need to report an AE.

Overlap of Local Laboratory Normal Values with Grading Table Ranges. When local laboratory normal values fall within grading table laboratory ranges, the severity grading is based on the ranges in the grading table unless there is a protocol-specific grading criterion for the laboratory value. For example, “Magnesium, Low" has a grade 1 range of 1.2 to < 1.4 mEq/L, while a particular laboratory’s normal range for magnesium may be 1.3 to 2.8 mEq/L. If a study participant’s magnesium laboratory value is 1.3 mEq/L, the laboratory value should be graded as grade 1.

Estimating Severity Grade for Parameters Not Identified in the Grading Table

The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) Specify type, if applicable	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities1 Hypertension (with the lowest reading taken after repeat testing during a visit) ≥ 18 years of age	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. *Pediatrics* 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.

Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction Report only one	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block Report only one > 16 years of age	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block or ventricular delay of 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block of ventricular delay of 3.0 seconds	Complete AV block

Prolonged QTc Interval2	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism Report only one	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA

[2] As per Bazett's formula.

Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Rash Specify type, if applicable	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

Endocrine and Metabolomic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar nonketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)

Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

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Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)

Diarrhea ≥ 1 year of age	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia Report only one and specify location	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis Report only one and specify location	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g.,

				circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskelatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING

Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] ≥ 30 years of age	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Osteoporosis6 ≥ 30 years of age	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see Cognitive, Behavioral, or Attentional Disturbance below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions

Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) Specify type, if applicable	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on parttime basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a fulltime basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay < 18 years of age Specify type, if applicable	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) Specify type, if applicable	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

	decreased strength on examination			
Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

Seizures New Onset Seizure ≥ 18 years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or preexisting febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without	Change in seizure character either in duration or quality	Prolonged and repetitive seizures (e.g., status epilepticus) OR

		change in seizure character	(e.g., severity or focality)	Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) Specify disorder	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt Report only one	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR	Suicide attempted

		specific plan or intent	Hospitalization indicated	

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress Report only one	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss ≥ 12 years of age	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speechlanguage related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR	Posterior or panuveitis OR Operative	Disabling visual loss in affected eye(s)

		Medical intervention indicated	intervention indicated	
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

Cytokine Release Syndrome7	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain8 (not associated with study agent injections and not specified elsewhere) Specify location	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated

[7] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[8] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).

Serum Sickness9	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight10 > 5 to 19 years of age	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO Weight-for-height z-score < -1 to -2	WHO Weight-for-height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with lifethreatening consequences
< 2 years of age	WHO Weight-for-length z-score < -1 to -2	WHO Weight-for-length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with lifethreatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

Urinary

[9] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.

[10] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness Report only one	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated

Injection Site Erythema or Redness11 Report only one > 15 years of age	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially lifethreatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially lifethreatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling Report only one > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age	Same as for Injection Site Erythema or Redness, > 15 years of age
≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age	Same as for Injection Site Erythema or Redness, ≤ 15 years of age

[11] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

Laboratory Values*

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without lifethreatening consequences	pH < 7.3 with lifethreatening consequences
Albumin, Low (g/dL; g/L)	3.0 to < LLN 30 to < LLN	≥ 2.0 to < 3.0 ≥ 20 to < 30	< 2.0 < 20	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without lifethreatening consequences	pH > 7.5 with lifethreatening consequences
ALT or SGPT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High Report only one	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; mmol/L)	16.0 to < LLN 16.0 to < LLN	11.0 to < 16.0 11.0 to < 16.0	8.0 to < 11.0 8.0 to < 11.0	< 8.0 < 8.0

Bilirubin Direct Bilirubin13, High > 28 days of age	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with lifethreatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates	See Appendix A. Total Bilirubin for Term and Preterm Neonates

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

13 Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; mmol/L) ≥ 7 days of age	10.6 to < 11.5 2.65 to < 2.88	11.5 to < 12.5 2.88 to < 3.13	12.5 to < 13.5 3.13 to < 3.38	≥ 13.5 ≥ 3.38
< 7 days of age	11.5 to < 12.4 2.88 to < 3.10	12.4 to < 12.9 3.10 to < 3.23	12.9 to < 13.5 3.23 to < 3.38	≥ 13.5 ≥ 3.38
Calcium (Ionized), High (mg/dL; mmol/L)	> ULN to < 6.0 > ULN to < 1.5	6.0 to < 6.4 1.5 to < 1.6	6.4 to < 7.2 1.6 to < 1.8	≥ 7.2 ≥ 1.8

Calcium, Low (mg/dL; mmol/L) ≥ 7 days of age	7.8 to < 8.4 1.95 to < 2.10	7.0 to < 7.8 1.75 to < 1.95	6.1 to < 7.0 1.53 to < 1.75	< 6.1 < 1.53
< 7 days of age	6.5 to < 7.5 1.63 to < 1.88	6.0 to < 6.5 1.50 to < 1.63	5.50 to < 6.0 1.38 to < 1.50	< 5.50 < 1.38
Calcium (Ionized), Low (mg/dL; mmol/L)	< LLN to 4.0 < LLN to 1.0	3.6 to < 4.0 0.9 to < 1.0	3.2 to < 3.6 0.8 to < 0.9	< 3.2 < 0.8
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High *Report only one	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance12 or eGFR, Low *Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; mmol/L) Fasting, High	110 to 125 6.11 to < 6.95	> 125 to 250 6.95 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75
Nonfasting, High	116 to 160 6.44 to < 8.89	> 160 to 250 8.89 to < 13.89	> 250 to 500 13.89 to < 27.75	≥ 500 ≥ 27.75

[12] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade.

Glucose, Low (mg/dL; mmol/L) ≥ 1 month of age	55 to 64 3.05 to <3.55	40 to < 55 2.22 to < 3.05	30 to < 40 1.67 to < 2.22	< 30 < 1.67
< 1 month of age	50 to 54 2.78 to < 3.00	40 to < 50 2.22 to < 2.78	30 to < 40 1.67 to < 2.22	< 30 < 1.67
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without lifethreatening consequences	Increased lactate with pH < 7.3 with lifethreatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; mmol/L) Cholesterol, Fasting, High ≥ 18 years of age	200 to < 240 5.18 to < 6.19	240 to < 300 6.19 to < 7.77	≥ 300 ≥ 7.77	NA
< 18 years of age	170 to < 200 4.40 to < 5.15	200 to < 300 5.15 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High ≥ 18 years of age	130 to < 160 3.37 to < 4.12	160 to < 190 4.12 to < 4.90	≥ 190 ≥ 4.90	NA
> 2 to < 18 years of age	110 to < 130 2.85 to < 3.34	130 to < 190 3.34 to < 4.90	≥ 190 ≥ 4.90	NA
Triglycerides, Fasting, High	150 to 300 1.71 to 3.42	>300 to 500 >3.42 to 5.7	>500 to < 1,000 >5.7 to 11.4	> 1,000 > 11.4
Magnesium13, Low (mEq/L; mmol/L)	1.2 to < 1.4 0.60 to < 0.70	0.9 to < 1.2 0.45 to < 0.60	0.6 to < 0.9 0.30 to < 0.45	< 0.6 < 0.30
Phosphate, Low (mg/dL; mmol/L) > 14 years of age	2.0 to < LLN 0.65 to < LLN	1.4 to < 2.0 0.45 to < 0.65	1.0 to < 1.4 0.32 to < 0.45	< 1.0 < 0.32

[13] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

1 to 14 years of age	3.0 to < 3.5 0.97 to < 1.13	2.5 to < 3.0 0.81 to < 0.97	1.5 to < 2.5 0.48 to < 0.81	< 1.5 < 0.48
< 1 year of age	3.5 to < 4.5 1.13 to < 1.45	2.5 to < 3.5 0.81 to < 1.13	1.5 to < 2.5 0.48 to < 0.81	< 1.5 < 0.48
Potassium, High (mEq/L; mmol/L)	5.6 to < 6.0 5.6 to < 6.0	6.0 to < 6.5 6.0 to < 6.5	6.5 to < 7.0 6.5 to < 7.0	≥ 7.0 ≥ 7.0
Potassium, Low (mEq/L; mmol/L)	3.0 to < 3.4 3.0 to < 3.4	2.5 to < 3.0 2.5 to < 3.0	2.0 to < 2.5 2.0 to < 2.5	< 2.0 < 2.0
Sodium, High (mEq/L; mmol/L)	146 to < 150 146 to < 150	150 to < 154 150 to < 154	154 to < 160 154 to < 160	≥ 160 ≥ 160
Sodium, Low (mEq/L; mmol/L)	130 to < 135 130 to < 135	125 to < 130 125 to < 130	121 to < 125 121 to < 125	≤ 120 ≤ 120
Uric Acid, High (mg/dL; mmol/L)	7.5 to < 10.0 0.45 to < 0.59	10.0 to < 12.0 0.59 to < 0.71	12.0 to < 15.0 0.71 to < 0.89	≥ 15.0 ≥ 0.89

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm3; cells/L) > 5 years of age (not HIV infected)	300 to < 400 300 to < 400	200 to < 300 200 to < 300	100 to < 200 100 to < 200	< 100 < 100
Absolute Lymphocyte Count, Low (cell/mm3; cells/L) > 5 years of age (not HIV infected)	600 to < 650 0.600 x 109 to < 0.650 x 109	500 to < 600 0.500 x 109 to < 0.600 x 109	350 to < 500 0.350 x 109 to < 0.500 x 109	< 350 < 0.350 x 109

Absolute Neutrophil Count (ANC), Low (cells/mm3; cells/L) > 7 days of age	800 to 1,000 0.800 x 109 to 1.000 x 109	600 to 799 0.600 x 109 to 0.799 x 109	400 to 599 0.400 x 109 to 0.599 x 109	< 400 < 0.400 x 109
2 to 7 days of age	1,250 to 1,500 1.250 x 109 to 1.500 x 109	1,000 to 1,249 1.000 x 109 to 1.249 x 109	750 to 999 0.750 x 109 to 0.999 x 109	< 750 < 0.750 x 109
≤ 1 day of age	4,000 to 5,000 4.000 x 109 to 5.000 x 109	3,000 to 3,999 3.000 x 109 to 3.999 x 109	1,500 to 2,999 1.500 x 109 to 2.999 x 109	< 1,500 < 1.500 x 109
Fibrinogen, Decreased (mg/dL; g/L)	100 to < 200 1.00 to < 2.00 OR 0.75 to < 1.00 x LLN	75 to < 100 0.75 to < 1.00 OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 0.50 to < 0.75 OR 0.25 to < 0.50 x LLN	< 50 < 0.50 OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin14, Low (g/dL; mmol/L)15 ≥ 13 years of age (male only)	10.0 to 10.9 6.19 to 6.76	9.0 to < 10.0 5.57 to < 6.19	7.0 to < 9.0 4.34 to < 5.57	< 7.0 < 4.34
≥ 13 years of age (female only)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03

Hematology

[14] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[15] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 5.88 to 6.48	8.5 to < 9.5 5.25 to < 5.88	6.5 to < 8.5 4.03 to < 5.25	< 6.5 < 4.03
36 to 56 days of age (male and female)	8.5 to 9.6 5.26 to 5.99	7.0 to < 8.5 4.32 to < 5.26	6.0 to < 7.0 3.72 to < 4.32	< 6.0 < 3.72
22 to 35 days of age (male and female)	9.5 to 11.0 5.88 to 6.86	8.0 to < 9.5 4.94 to < 5.88	6.7 to < 8.0 4.15 to < 4.94	< 6.7 < 4.15
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 6.81 to 8.10	9.0 to < 11.0 5.57 to < 6.81	8.0 to < 9.0 4.96 to < 5.57	< 8.0 < 4.96
≤ 7 days of age (male and female)	13.0 to 14.0 8.05 to 8.72	10.0 to < 13.0 6.19 to < 8.05	9.0 to < 10.0 5.59 to < 6.19	< 9.0 < 5.59
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm3; cells/L)	100,000 to < 125,000 100.000 x 109 to < 125.000 x 109	50,000 to < 100,000 50.000 x 109 to < 100.000 x 109	25,000 to < 50,000 25.000 x 109 to < 50.000 x 109	< 25,000 < 25.000 x 109
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm3; cells/L) > 7 days of age	2,000 to 2,499 2.000 x 109 to 2.499 x 109	1,500 to 1,999 1.500 x 109 to 1.999 x 109	1,000 to 1,499 1.000 x 109 to 1.499 x 109	< 1,000 < 1.000 x 109

≤ 7 days of age	5,500 to 6,999 5.500 x 109 to 6.999 x 109	4,000 to 5,499 4.000 x 109 to 5.499 x 109	2,500 to 3,999 2.500 x 109 to 3.999 x 109	< 2,500 < 2.500 x 109

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A. Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING

Total Bilirubin16, High (mg/dL; µmol/L)17 Term Neonate18 < 24 hours of age	4 to < 7 68.4 to < 119.7	7 to < 10 119.7 to < 171	10 to < 17 171 to < 290.7	≥ 17 ≥ 290.7
24 to < 48 hours of age	5 to < 8 85.5 to < 136.8	8 to < 12 136.8 to < 205.2	12 to < 19 205.2 to < 324.9	≥ 19 ≥ 324.9
48 to < 72 hours of age	8.5 to < 13 145.35 to < 222.3	13 to < 15 222.3 to < 256.5	15 to < 22 256.5 to < 376.2	≥ 22 ≥ 376.2
72 hours to < 7 days of age	11 to < 16 188.1 to < 273.6	16 to < 18 273.6 to < 307.8	18 to < 24 307.8 to < 410.4	≥ 24 ≥ 410.4
7 to 28 days of age (breast feeding)	5 to < 10 85.5 to < 171	10 to < 20 171 to < 342	20 to < 25 342 to < 427.5	≥ 25 ≥ 427.5
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate20 35 to < 37 weeks gestational age	Same as for Total Bilirubin, High, Term Neonate (based on days of age).	Same as for Total Bilirubin, High, Term Neonate (based on days of age).	Same as for Total Bilirubin, High, Term Neonate (based on days of age).	Same as for Total Bilirubin, High, Term Neonate (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 171 to < 239.4	≥ 14 ≥ 239.4
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 102.6 to < 171	≥ 10 ≥ *171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 85.5 to < 136.8	≥ 8 ≥ *136.8*

[16] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[17] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[18] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

7 to 28 days of age (breast feeding)	5 to < 10 85.5 to < 171	10 to < 20 171 to < 342	20 to < 25 342 to < 427.5	≥ 25 ≥ 427.5
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

12.4 APPENDIX 4. IRB REPORTING

This guidance applies to Stanford University human subject research and details events or circumstances that must be promptly reported to the IRB during the conduct of human subject research.

Events and information which require prompt reporting to the IRB

1) Unanticipated Problems Involving Risks to Participants or Others (UPs)

Events (internal or external, deaths, life-threatening experiences, injuries, or other) occurring during the research study, which in the opinion of the Monitoring Entity or the PD meet all of the following criteria:

- Unexpected

in terms of nature, severity, or frequency, given (a) the research procedures described in the protocol-related documents such as the IRB-approved research protocol and informed consent document or the Investigator's Brochure, and (b) the characteristics of the subject population being studied;

AND

- Related or Possibly Related to participation in the research or there is a reasonable possibility or likelihood that the incident, experience, or outcome may have been caused by the procedures involved in the research;

AND

- Places Subjects or Others at a Greater Risk of Harm

the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm, including harm related to breaches of privacy) than was previously known or recognized.

NOTE:

- A “UP” generally will warrant consideration of substantive changes in the research protocol or informed consent process/document, or other corrective actions, in order to protect the safety, welfare, or rights of subjects or others.

2) **New Information** that indicates a change to the risks or potential benefits of the research in terms of severity or frequency or impacts the subject's willingness to participate (e.g., DSMB/DSMC Report, other safety information or publication, suspension or premature termination by the sponsor or investigator).

3) **Noncompliance**: An action, inaction, or activity, whether by the investigator, study staff, or others involved in human subject research, that is at variance with the approved IRB protocol, other requirements and determinations of the IRB, the HRPP Policy Manual and other applicable policies of Stanford University, SHC, LPCH, VAPAHCS (e.g., VHA Handbook 1200.5), Palo Alto Veterans Institute for Research (PAVIR) or relevant state or federal laws. The following are always considered noncompliance: human subjects research conducted without IRB approval, or approved by an outside IRB, without prior notice to Stanford's IRB (or Stanford IRB approval, if required under Stanford policies); or change(s) to the research implemented without IRB approval except when necessary to eliminate apparent immediate hazards to the subject.

   When the event is:

   - Possibly serious: Any behavior, action, inaction, or omission in the conduct or oversight of human research that, in the judgment of the IRB, has been determined to:
     - adversely affect or compromise the rights or welfare of participants;
     - harm or materially increase exposure to significant risk of harm to a research participant(the IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance);
     - result in a detrimental change to a participant's clinical or emotional condition or status; or
     - compromise the integrity or validity of the research.

   - Possibly continuing: A pattern of repeated instances of noncompliance that:
     - Continues to occur after discovery of noncompliance or implementation of a preventive action plan; or
     - Results from failure to implement a preventive action plan approved by the IRB; or
     - A circumstance in which an investigator or other study staff fails to cooperate with investigating or correcting non-compliance.

4) **Complaint** unresolved by the research team

5) **Incarceration** when in the opinion of the PD it is in the best interest of the participant to remain on the study.

6) **Unanticipated adverse device effect (UADE)**

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. 21 CFR 812.3(s)

7) Other events or information

Examples include: a deviation intended to eliminate an immediate hazard to a participant, suicide or suicide attempt of a participant, other Audit or Monitoring Visit reports and Corrective Action Preventative Action (CAPA) plans. Report only after consulting with the IRB Panel Manager.

Timeframes

- Timeframe for UP reports depends on Monitoring Entity
    - If PD is the only monitoring entity
      Items 1 - 6 should be reported directly to the IRB within 10 working days from when the PD learns of the event or new information.
    - If there is a monitoring entity in addition to, or other than, the PD
      Report to the IRB using this form within 10 working days from receiving assessment from monitoring entity. The PD should report to the IRB when the event has been assessed by the monitoring entity to be a UP.
- Timeframe for Reportable Information (items 2 - 7)
  These should always be reported by the PD directly to the IRB within 10 working days from when the PD learns of the event or new information.
- Unexpected deaths or life-threatening experiences related to the research (at Stanford, or when STANFORD is the coordinating institution in a multi-site study) must be reported to the IRB within 5 working days from PD learning of event.

12.5 APPENDIX 5. GENETICS

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
    - Retained samples will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.