9.1.1 Protocol and Protocol Amendments

This section includes the following:

Original	07 July 2022
Amendment 1 Summary of Changes	26 August 2022
Amendment 1	26 August 2022
Clarification Letter 1	30 September 2022
Administrative Letter 1	31 October 2022
Administrative Letter 2	17 November 2022
Clarification Letter 2	10 February 2023
Protocol Termination Letter	10 April 2023

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19
Sponsor:	Pardes Biosciences, Inc. 2173 Salk Avenue PMB #052 Carlsbad, CA 92008
IND Number:	158228
EudraCT Number:	2022-001195-33
ClinicalTrials.gov Identifier:	Not available
Indication:	Treatment and prevention of SARS-CoV-2 infection and associated diseases (ie, COVID-19)
Protocol ID:	PBI-0451-0002
Contact Information:	The medical monitor's name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original 07 July 2022

CONFIDENTIALITY STATEMENT

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration (2021)
CL_{CR}	creatinine clearance
CoV	coronavirus
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CVAP	Clinical Virology Analysis Plan
CYP	cytochrome P450
DAA	direct-acting antiviral
DDI	drug-drug interaction
EC_{50}	concentration (or dose) effective in producing 50% of the maximal response
EC_{90}	concentration (or dose) effective in producing 90% of the maximal response
ECG	electrocardiogram
(e)CRF	(electronic) case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination (visit)
GCP	Good Clinical Practice
GPCR	G protein-coupled receptor
HBV	hepatitis B virus
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCoV	human coronavirus
HCV	hepatitis C virus
HIV(-1)	human immunodeficiency virus (Type 1)
IB	Investigator's Brochure
ICF	informed consent form

ICH	International Conference for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
IVA	infectious virus assay
IXRS	interactive voice and web response system
LOD	limit of detection
mAb	monoclonal antibody
MERS	Middle Eastern respiratory syndrome
(m)ITT	(modified) intention-to-treat
M^{pro}	main protease
MT	mid-turbinate
NAAT	nucleic acid amplification test
PK	pharmacokinetic(s)
P-gp	P-glycoprotein
PTM	placebo-to-match
PVE	pharmacovigilance
(q)RT-PCR	(quantitative) reverse transcriptase polymerase chain reaction
RAT	rapid antigen test
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
$TCID_{50}$	median tissue culture infectious dose

PROTOCOL SYNOPSIS

Pardes Biosciences, Inc.
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Study Title: A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19

IND Number: IND 158228

EudraCT Number: 2022-001195-33

Study Centers Planned: Up to 100 study centers are planned.

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the antiviral activity of PBI-0451	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA)
Secondary Objectives	**Secondary Endpoint**
• To evaluate safety and tolerability of PBI-0451	• Number of treatment-emergent adverse events (AEs), serious adverse events (SAEs), discontinuation due to AEs, and Grade 3 or 4 laboratory abnormalities
• To evaluate clinical efficacy of PBI-0451 versus placebo through study Day 28	• Proportion of subjects with sustained symptom resolution through Day 28 • Time to sustained symptom resolution through Day 28 • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 • Severity of targeted COVID-19 symptoms

	• Number of COVID-19 related medical visits other than hospitalization, including acute/critical care visits through Day 28 • Number of days in any hospital unit for treatment of COVID-19
• To evaluate the effect of PBI-0451 on SARS-CoV-2	• Presence of SARS-CoV-2 infection based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate SARS-CoV-2 resistance to PBI-0451	• Sequence analysis of the SARS-CoV-2 main protease (M^{pro}) gene (nsp5) and M^{pro} cleavage sites
• To evaluate SARS-CoV-2 resistant variant susceptibility to PBI-0451	• Susceptibility analysis of SARS-CoV-2 variants with M^{pro} amino acid substitutions and variants with substitutions in M^{pro} cleavage sites in the SARS-CoV-2 polyprotein
• To evaluate the relationship between SARS-CoV-2 detection methods	• Correlation of SARS-CoV-2 detection by IVA, RAT, and qRT-PCR, as specified in the CVAP
• To evaluate the incidence of rebound SARS-CoV-2 infection	• Proportion of subjects with clinical and/or virologic rebound
• To evaluate PBI-0451 pharmacokinetics (PK)	• PBI-0451 PK analysis from an intensive PK substudy of up to 50 subjects • PK parameters from sparse sampling of all subjects for population PK analysis
Study Design: Phase 2, double-blind, randomized, placebo-controlled study	
Number of Subjects Planned: Approximately 210 subjects will be randomized.	

Target Population: Nonhospitalized, symptomatic male and nonpregnant, nonlactating female subjects 18 to < 65 years of age with a positive direct test of SARS-CoV-2 infection (antigen based or nucleic acid amplification test [NAAT]) who are not at high-risk of progressing to severe disease

Duration of Treatment: 5 days

Study Duration: Up to 28 days of assessments (ie, the study period) and a Week 24 follow-up to assess symptoms and survival status

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

1. Can understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of any study procedures.
2. Onset of COVID-19 symptoms ≤ 5 days prior to randomization with a positive SARS-CoV-2 test ≤ 24 hours prior to randomization. Authorized NAAT or antigen tests that detect viral RNA or protein, respectively, are allowed.
3. ≥ 2 symptoms of acute COVID-19 infection as determined by the investigator from the symptoms listed on the COVID-19 symptoms questionnaire present at randomization
4. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or > 2 years post menopause.
5. Male and female subjects and/or their heterosexual partners must either be of nonchildbearing potential or must use effective contraception from screening through 90 days after the last dose of study drug
6. Female subjects must refrain from egg donation and in vitro fertilization during treatment and for ≥ 28 days after the last dose of study drug
7. Male subjects must refrain from sperm donation from screening through 90 days after the last dose of study drug
8. Normal 12-lead electrocardiogram (ECG) evaluation without clinically significant abnormalities
9. Able and willing to comply with all study requirements

Exclusion Criteria

10. If unvaccinated, ≥ 1 Centers for Disease Control and Prevention defined underlying medical condition associated with an increased risk of developing severe illness from COVID-19

11. ≥ 1 SARS-CoV-2 vaccination (including a booster) within 3 months prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period
12. Currently hospitalized or expected to require hospitalization for COVID-19 within 48 hours of randomization
13. Currently being treated or expected to be treated for COVID-19 with monoclonal antibodies, convalescent serum, or direct-acting antiviral agents
14. Any clinical condition or laboratory result considered by the investigator to indicate any unstable or poorly controlled underlying clinically significant medical condition(s), active disseminated infection (other than SARS-CoV-2), or other medical condition that could represent a risk to the subject, including increasing the likelihood of a safety event, affect subject compliance, or affect efficacy and/or safety data collected during the 28-day study period
15. Known active liver disease, including nonalcoholic steatohepatitis/nonalcoholic fatty liver disease, chronic or active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, primary biliary cirrhosis, Child-Pugh Class B or C, chronic alcoholic liver disease, or acute liver failure
16. Receiving dialysis or having known severe renal impairment (chronic kidney disease, Stage 4 or above)
17. Unable or unwilling to comply with the protocol procedures
18. Participating in another interventional study with an investigational compound or device, including those for COVID-19
19. Known prior participation in this study or another study involving PBI-0451
20. Females who are pregnant or breastfeeding
21. Oxygen saturation of < 94% on room air

Study Procedures/Frequency: Following completion of screening and eligibility assessments, eligible subjects will be randomized 2:1 to one of 2 treatment groups on Day 1 as follows:

- PBI-0451: 2 × 350 mg tablets administered orally twice daily (BID) (1400 mg/day) with food for 5 days (10 total doses)
- Placebo: 2 × placebo to match PBI-0451 tablets administered orally BID with food for 5 days (10 total doses)

Randomization will be stratified as follows:

- SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization
- Vaccinated (ie, ≥ 1 dose of an approved vaccine) versus unvaccinated
- PK substudy participation versus nonparticipation

Note: Screening assessments may be considered as baseline/Day 1 assessments if the subject meets eligibility requirements, is randomized, and receives the first dose of study drug on same day.

Study Visits: Following randomization on Day 1, subjects will complete baseline assessments prior to receiving their first dose of study drug (PBI-0451 or placebo). All subjects will have additional safety and efficacy assessments during the 28-day study period.

A follow-up visit (eg, telephone, televisit, clinic visit, etc**.** as convenient) will be conducted at Week 24 (± 20 days) after the last dose of study drug for all subjects. Information regarding ongoing or recurrent COVID-19 symptoms, survival status, pregnancy status (for female subjects of childbearing potential and female partners of male subjects), and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) that have occurred since the last study visit will be collected.

Study Drug Administration: Subjects will take their first dose of study drug (PBI-0451 or placebo) with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1 to ensure that a full total daily dose (1400 mg PBI-0451) is taken on the first day of treatment. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of 5 days of treatment.

Patient-Reported Outcomes: Subject self-reports will be assessed daily at screening, Days 1 through 28 or early termination (ET), and the Week 24 follow-up as follows:

- COVID-19 symptom questionnaire
- COVD-19 related hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) since the last study visit

  Hospitalization is defined as > 24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19. This includes any special medical care unit within an assisted living facility or nursing home.

- Optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members (baseline/Day 1 and Days 5, 10, 15, and 28 or ET only)

Serology Testing: Serology samples at screening and/or baseline/Day 1:

- SARS-CoV-2 (using the Roche Elecsys® Anti-SARS-CoV-2 assay)
- Human immunodeficiency virus Type 1
- HBV (hepatitis B serum antigen; hepatitis B core antibody)
- HCV (hepatitis C antibody, reflex to HCV RNA)

Virologic Assessments: The following tests will be performed from mid-turbinate (MT) nasal swab and saliva samples at screening, baseline/Day 1, and Days 2, 3, 5, 10, 15, and 28 or early termination (ET)

- SARS-CoV-2 qRT-PCR (MT swab and saliva)

- SARS-CoV-2 RAT (MT swab)
- SARS-CoV-2 IVA (MT swab and saliva) at baseline/Day 1 and Days 2, 3, 5, and 10 only
- SARS-CoV-2 sequence analysis (MT swab) at baseline/Day 1 and Day 5 for all subjects to evaluate the potential for the development of resistance in response to treatment with PBI-0451. Additional time points may be evaluated in the case of virologic rebound or if the subject remains viremic through Day 28 (ie, if SARS-CoV-2 RNA by qRT-PCR is ≥ 3.85 $\log_{10}$ copies/mL, which is the threshold for the minimum amount of viral RNA required for whole genome sequencing).

RAT will be conducted for subjects at the study clinic with results recorded in real time. All other MT and saliva samples will be shipped to the central laboratory on the day of collection for subsequent qRT-PCR and IVA testing.

Note: SARS-CoV-2 RAT or qRT-PCR tests for household members will not be performed at the study clinic; that data will be captured as part of an optional self-reported assessment of confirmed SARS-CoV-2 infections in household members.

Safety Assessments:

- Complete physical examination: Screening and baseline/Day 1 and Day 28 or ET
- Symptom-driven physical examination: Days 2, 3, 5, 10, and 15
- Vital signs: All visits
- 12-lead ECG: Screening; baseline/Day 1 (predose;) and Days 5, 10, and 28 or ET
- Clinical laboratory blood draws (hematology and chemistry) and urinalysis: baseline/Day 1 (predose) and Days 5, 10, and 28 or ET
- Serum/urine pregnancy test (females of childbearing potential only): Screening, baseline/Day 1, and Day 28 or ET

AEs and concomitant medications will be monitored throughout the study, including worsening of COVID-19 symptoms per the COVID-19 symptoms questionnaire and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility).

Pharmacokinetic Assessments:

- All subjects will have single PK blood draws at baseline/Day 1 (after first dose of study drug) and Day 5, with the time of the blood draw relative to the last dose of study drug recorded.
- An intensive PK substudy will be conducted in a subset of up to 50 subjects at select sites who provide separate specific consent. Intensive PK blood draws will be collected at the following time points: predose (ie, ≤ 5 minutes of dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and (optional) 10 to 12 hours postdose. Intensive PK sampling may occur on any treatment day (ie, baseline/Day 1 [after first dose of study drug] through Day 5).

Any remaining PK samples will be stored and may be used for exploratory assessments, such as metabolites, protein binding, endogenous markers of drug-drug interactions, biomarkers of host responsiveness, and other investigational experiments.
Test Product, Dose, and Mode of Administration: 2 × 350 mg tablets administered orally BID (1400 mg/day) with food for 5 days (10 total doses) Subjects will take their first dose with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1 to ensure that a full total daily dose (1400 mg PBI-0451) is taken on the first day of treatment. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of 5 days of treatment
Reference Therapy, Dose, and Mode of Administration: 2 × placebo to match PBI-0451 tablets administered orally BID for 5 days (10 total doses). Subjects will take their first dose with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of 5 days of treatment
Statistical Methods: Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. Summary statistics will be used to analyze the study data. Any statistical testing will be conducted to ensure that the overall alpha = 0.05 level (2 sided). Unless otherwise specified, the data summaries and analyses described below will be reported by treatment group. The modified intention-to-treat (mITT) analysis set includes all randomized subjects with ≥ 2 symptoms consistent with COVID-19 ≤ 5 days prior to randomization and a positive SARS-CoV-2 test (RT-PCR or RAT) ≤ 24 hours prior to randomization who received ≥ 1 dose of study drug. This is the primary analysis set for all clinical endpoints. The mITT virologic analysis set is a subset of the mITT analysis set that includes subjects who had detectable infectious SARS-CoV-2 by IVA at baseline/Day 1. This is the primary analysis set for the primary efficacy endpoint. **Efficacy:** The primary efficacy endpoint is the proportion of subjects below the LOD for infectious SARS-CoV-2 on Day 3 by IVA. For the primary endpoint, differences between PBI-0451 and placebo will be evaluated using stratum-adjusted Mantel-Haenszel proportions (adjusted for randomization strata). The proportion of subjects below the LOD for infectious SARS-CoV-2 at other time points will be summarized in a similar manner. The time to resolution of targeted COVID-19 symptoms will be estimated with the Kaplan-Meier method and summarized by treatment group. Differences between treatment groups will be determined using a Wilcoxon-Gehan test. The analysis of time to resolution of each targeted COVID-19 symptom will be conducted in a similar manner.

The proportion of subjects with COVID-19 related hospitalization or death from any cause will be summarized by treatment group. Differences between treatment groups will be assessed using Mantel-Haenszel proportions.

The number of COVID-19 related hospitalizations or acute/critical care visits and the number of days in any hospital unit for the treatment of COVID-19 will be summarized. Differences between treatment groups will be assessed using a van Elteren test stratified by the randomization factors.

SARS-CoV-2 viral load kinetics will be summarized by study visit. Differences between the treatment groups will be assessed with a van Elteren test stratified by the randomization factors.

SARS-CoV-2 clinical and virologic rebound will be summarized by the amount of viral RNA detected at baseline/Day 1, time to loss of clinical symptoms, time to negative RAT or IVA, and time to the first confirmed reappearance of symptoms and/or a positive RAT or qRT-PCR sample.

A correlation of the results of IVA, RAT, and qRT-PCR assessments will be evaluated.

Virologic outcomes will be summarized by subject serology status determined using the Roche Elecsys Anti-SARS-CoV-2 assay, which uses a recombinant protein representing the nucleocapsid (N) antigen to detect antibodies against SARS-CoV-2.

Safety: The safety analysis set includes all randomized subjects who received ≥ 1 dose of study drug. This is the primary analysis set for safety analyses.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs, SAEs, and AEs leading to premature discontinuation of study drug/study will be summarized by treatment, system organ class, and preferred term.

Laboratory results and change from predose values for selected laboratory tests will be summarized by treatment at scheduled visits. The incidence of treatment-emergent laboratory abnormalities (Division of AIDS Toxicity Grading Scale) will be summarized by treatment.

Pharmacokinetics: The PK analysis set includes all subjects who participated in the intensive PK substudy and have ≥ 1 nonmissing PK concentration reported by the PK laboratory. This is the primary analysis set for PK analyses.

PBI-0451 plasma concentrations and PK parameters will be derived using noncompartmental methods (including metabolite[s] as applicable) and listed and summarized using descriptive statistics.

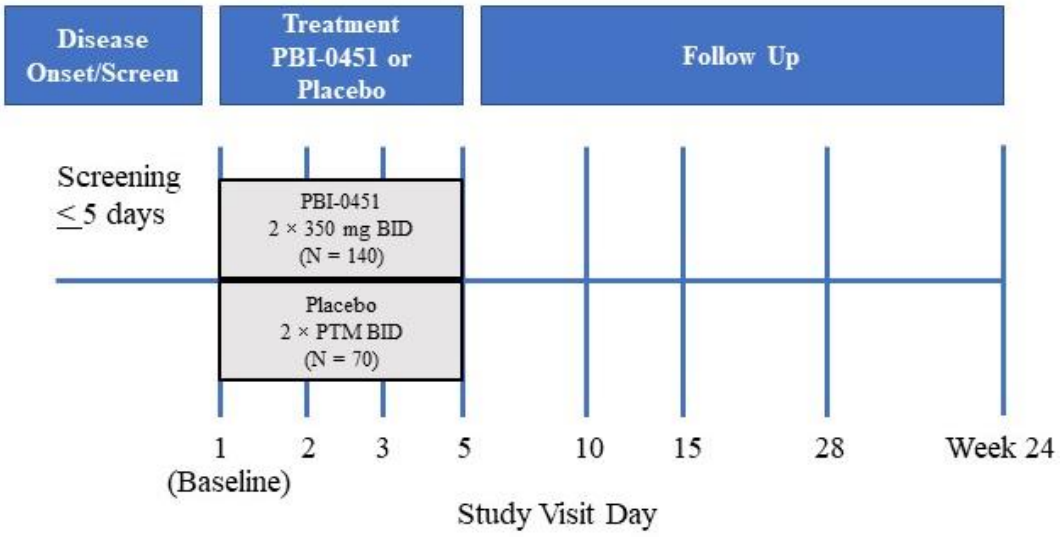
PBI-0451 plasma concentrations from the PK substudy and sparse sampling from the overall study population will be used in a population PK analysis and reported separately.

Sample Size: The sample size will be approximately 210 subjects to account for approximately 60% of randomized subjects who are anticipated to be SARS-CoV-2 negative by IVA at baseline/Day 1 and would be excluded from the mITT virologic analysis set. It should be noted that this sample size is sufficient with ≥ 80 power to detect a > 19% absolute difference in the proportion of subjects below the LOD for infectious SARS-CoV-2 virus (99%

vs 81%) at Day 3 by IVA among subjects who had detectable infectious SARS-CoV-2 at baseline/Day 1. This assumes alpha = 0.05 and that 40% of subjects have detectable infectious virus at baseline/Day 1.

STUDY SCHEMA

Figure 1. Study PBI-0451-0002: Study Schema



BID = twice daily; PTM = placebo to match

STUDY PROCEDURES TABLE

Table 1. Study PBI-0451-0002: Study Procedures Table

	Screening[a] (Day -5 to Day 1)	Baseline/Day 1[b]	Day 2 (±1 day)[c]	Day 3 (±1 day)[c]	Day 5 (±1 day)[c]	Day 10 (±2 days)	Day 15 (±2 days)	Rebound Ad Hoc Visit[d]	Day 28 (±3 days)	Week 24 Follow Up (±20 days)[e]	ET
Written Informed Consent	X										
Medical History	X										
Complete Physical Examination	X	(X)							X		X
Symptom-Driven Physical Examination			X	X	X	X	X	X			
Height	X	(X)									
Weight	X	(X)							X		X
Vital Signs[f]	X	(X)	X	X	X	X	X		X		X
SARS-CoV-2 N-antibodies	X	(X)									
SARS-CoV-2 RAT[g]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 qRT-PCR Test[g]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 Sequence Analysis[g,h]	X	(X)	(X)	(X)	X	(X)	(X)	X	(X)		(X)
SARS-CoV-2 IVA[g]	X	(X)	X	X	X	X					(X)
HIV-1, HBV (HbsAg and HbcAb), and HCV (HCV antibody reflex to HCV RNA) Testing	X	(X)									
12-Lead ECG	X	(X)			X	X			X		X
Optional Genomic Sample		X									
Hematology[i]		X			X	X			X		X

	Screening[a] (Day -5 to Day 1)	Baseline/Day 1[b]	Day 2 (±1 day)[c]	Day 3 (±1 day)[c]	Day 5 (±1 day)[c]	Day 10 (±2 days)	Day 15 (±2 days)	Rebound Ad Hoc Visit[d]	Day 28 (±3 days)	Week 24 Follow Up (±20 days)[e]	ET
Coagulation Panel		X			X	X			X		X
Chemistry[j]		X			X	X			X		X
Urinalysis[k]		X			X	X			X		X
Creatinine Clearance and eGFR		X			X	X			X		X
Serum/Urine Pregnancy Test[l]	X	(X)							X		X
Study Drug Dispensing		X									
Study Drug Administration		2 × 350 mg PBI-0451 or Placebo BID orally for 5 days (10 total doses)									
Patient Reported Outcomes[m]	X	(X)	X							X	X
Intensive PK Sampling[n]		X									
Single PK Sample[o]		X			X						
Household Transmission Survey[p]		X			X	X	X		X		X
Survival Status[q]					X	X	X		X	X	
Review and Assess AEs and Concomitant Medication[r]	X	(X)	X	X	X	X	X	X	X		X

AE = adverse event; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HbcAb = hepatitis B core antibody; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus Type 1; IVA = infectious virus assay; PK = pharmacokinetics; qRT-PCR = quantitative reverse-transcriptase polymerase chain reaction; RAT = rapid antigen test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

a. Prospective subjects should be screened ≤ 5 days prior to administration of first dose of study drug (ie, randomization/Day 1)
b. Screening assessments may be considered as baseline/Day 1 if the subject is eligible for the study and is randomized and receives the first dose of study drug on that day. Parentheses indicate that assessment is not required if performed at screening, and screening and baseline/Day 1 are the same.
c. Individual study visits must occur on separate calendar days within the visit window, with the time(s) of sample collection recorded.

d. Subjects who experience a relapse in symptom(s) after having no COVID-19 symptom(s) for ≥3 days or have a positive RAT (or clinic qRT-PCR test) after testing negative by RAT or qRT-PCR will be requested to return to clinic within 2 days for mid-turbinate nasal swab and saliva samples for RAT, qRT-PCR, and sequencing.
e. Week 24 visit performed via telephone, televisit, or clinic visit, as convenient.
f. Vital signs include blood pressure, heart rate, respiratory rate, and temperature (predose and postdose on Day 1).
g. Mid-turbinate nasal swabs will be collected to measure SARS-CoV-2 using qRT-PCR, IVA, RAT, and viral sequencing. Saliva samples will be collected to measure SARS-CoV-2 using qRT-PCR and IVA. Parentheses indicate sample at ET visit if the subject discontinues treatment prior to Day 10.
h. SARS-CoV-2 sequence analysis (nasal mid-turbinate sample) will be conducted only if the subject is viremic and above the limit of detection (LOD) of the sequencing assay. Sequence analysis may be conducted on samples obtained at other study visits for subjects who experience virologic rebound or if the subject remains viremic through Day 28. Parentheses indicate sequencing samples where sequencing is dependent on the subject being viremic and experiencing virologic rebound and viral RNA is above the LOD of the sequencing assay by qRT-PCR.
i. Hematology includes complete blood count with differential and platelets.
j. Serum chemistry includes comprehensive metabolic panel.
k. Urinalysis includes microscopic reflex.
l. Pregnancy tests for females of childbearing potential only; screening urine test required for eligibility.
m. Self-reported daily assessment of targeted COVID-19 symptoms (per the COVID-19 symptoms questionnaire) and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) will be assessed daily at screening and from baseline/Day 1 through Day 28.
n. Intensive PK sampling for substudy subjects only. Sampling will occur relative to study drug administration at the following times: predose (ie, ≤ 5 minutes prior to dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and (optional) 10-12 hours postdose; intensive PK sampling will occur on any day of treatment from Day 1 (subject's first dose of study drug) to Day 5.
o. Sparse PK samples will be obtained at baseline/Day 1 (subsequent to subject's first dose of study drug) and Day 5.
p. Optional subject self-reported assessment of number of confirmed SARS-CoV-2 infections (RAT or qRT-PCR) in household members. No specific identifying information will be collected.
q. Survival status also includes current supplemental oxygen use, pregnancy status (for female subjects of childbearing potential and female partners of male subjects), and any hospitalizations or acute/critical care visits that occurred since the last study visit during the 28-day study period.
r. All AEs recorded from the time of obtaining informed consent through Day 28; all ongoing AE's will be followed to resolution or condition is considered permanent.

1. INTRODUCTION

1.1. Background

Pardes Biosciences, Inc. (hereafter referred to as Pardes) is developing PBI-0451, a new chemical entity and orally bioavailable direct-acting antiviral (DAA) inhibitor of the main protease (M^{pro}) of coronaviruses (CoVs), including the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes Coronavirus Disease 2019 (COVID-19) (Jin et al. 2020). PBI-0451 is an investigational agent that, by inhibiting the ability of the virus to replicate, has the potential for use as treatment and prevention of SARS-CoV-2 infection and associated diseases (ie, COVID-19). Additionally, it is anticipated that an effective DAA may reduce the magnitude and duration of viral shedding of replicating virus and therefore reduce the likelihood of transmission of SARS-CoV-2.

CoVs are positive, single-stranded RNA viruses, of which 7 infect humans and are believed to result in 5% to 30% of "common colds" for which therapeutic intervention is generally limited to over-the-counter symptomatic relief (Paules et al. 2020). CoV infection in humans is transmitted from person to person via shedding of replicating virus within the respiratory tract through aerosolization (Tang et al. 2020). SARS-CoV-2 is a novel strain of CoV discovered in late 2019 and responsible for COVID-19 that can range from mild to severe disease with symptoms, including extreme fatigue and dyspnea, that can be short-lived or prolonged (eg, "long COVID") with some cases developing pneumonia that can progress into acute respiratory distress syndrome and sometimes death, despite aggressive supportive care (Tang et al. 2020) (Sharma et al. 2020) (Marshall 2020). All persons are at risk for infection with SARS-CoV-2 and developing COVID-19. SARS-CoV-2 represents the third novel CoV (in addition to SARS-Co-V and Middle Eastern respiratory syndrome [MERS] CoV) to make a zoonotic transfer in the last 2 decades and result in significant human disease (Dhama et al. 2020). The potential for new CoV outbreaks is likely to continue.

Natural history data for nonpandemic CoV infection has established that reinfection with the same or different strains of CoV (including SARS-CoV-2) can occur (Tillett et al. 2021) (Harvey et al. 2021). Moreover, throughout the pandemic, surveillance has identified multiple spike protein mutations resulting in the global emergence of several SARS-CoV-2 variants of concern (ie, Delta, Omicron) due to potentially higher levels of transmissibility or immune escape (Korber et al. 2020) (Campbell et al. 2021) (Zella et al. 2021). This is particularly important as CoVs are known to mutate and undergo genetic recombination, which may facilitate transmission, replicative fitness, and pathogenicity across species (Lau and Chan 2015). A consequence of this has already been seen with some monoclonal antibodies (mAbs), where reduced efficacy against emerging SARS-CoV-2 variants (ie, Delta, Omicron) has led to recommendation against their use.

Near-universal vaccination is desired to reduce transmission and severity of COVID-19 disease; however, access to and acceptance of vaccines are suboptimal, and it is unknown if vaccines will

provide adequate duration of protection against current and future SARS-CoV-2 variants (Edridge et al. 2020).

While the details of the pathobiology and risk factors for developing severe COVID-19 disease remain unclear, it is established that early intervention to inhibit viral replication provides clinical benefit. Experience with influenza and emerging evidence with COVID-19 indicates that early treatment via a short course (eg, 5 days) of oral DAA therapy results in less severe disease and that preventing transmission is also possible (Muthuri et al. 2014) (Uyeki et al. 2019) (Chow et al. 2019) (Ikematsu et al. 2020).

Orally administered small molecule protease inhibitors are a clinically validated treatment and a standard of care for multiple viral diseases, including hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections (Ghany and Morgan 2020) (Department of Health and Human Services 2022). These agents can exhibit favorable drug-like properties and a favorable benefit:risk profile, including when used at high doses and exposures in both the short-term (weeks to months in HCV) and chronic (life-long therapy for HIV) settings (Patick and Potts 1998).

Small molecule DAAs that are orally administered and suitable for outpatient use are needed to treat people who become infected and are at high risk for severe COVID-19. In addition, treatment with oral DAAs is warranted to reduce the time to symptom resolution and decrease the duration of shedding infectious virus. Moreover, such agents can also be deployed in "ring prophylaxis" to contacts of infected individuals or in the setting of mitigating the spread of new, localized outbreaks. Small molecule oral DAAs are attractive therapeutics as they target viral and not host processes that may reduce the risk for off-target effects, and thus increase the likelihood of a favorable therapeutic index. Consequently, there remains a high unmet medical need for an easy to use, oral antiviral drug for the treatment and prevention of SARS-CoV-2 infection and associated diseases (ie, COVID-19).

1.2. PBI-0451

1.2.1. General Information

PBI-0451 is an investigational agent that has the potential for use as treatment and prevention SARS-CoV-2 infection and associated diseases (ie, COVID-19) by inhibiting the ability of the virus to replicate and thereby reduce the incidence and magnitude of the pathologic immune response responsible for the morbidity and mortality associated with severe disease. PBI-0451 is a potent inhibitor of SARS-CoV-2 M^{pro}, an essential enzyme for viral replication with EC_{50} = 23 nM and EC_{90} = 113.5 nM in SARS-CoV-2 antiviral assays. In nonclinical studies, PBI-0451 has broad-spectrum activity against SARS-CoV-2 clinical variants Alpha, Beta, Delta, Epsilon, Gamma, Mu, and Omicron and human coronaviruses (HCoVs) 229E and OC43 in cell-based antiviral assays. It has broad-spectrum activity in in vitro enzyme assays against the M^{pro} from HCoVs SARS, 229E, HKUI, OC43, NL63, and MERS, suggesting that it interacts with the

most essential elements of the M^{pro} binding pocket. This hypothesis is supported by in vitro resistance studies which suggest that PBI-0451 has a high barrier to resistance. In in vivo pharmacodynamic animal model of infection studies in mice, PBI-0451 showed a trend towards improved lung function at the higher PBI-0451 doses that correlated with a 10-fold decrease in viral load in the lung. Screens for off-target activity on host cysteine proteases and other targets revealed no significant concerns. A ritonavir (RTV)-boosted SARS-CoV-2 protease inhibitor targeting the same active enzyme pocket has shown significant benefit for high risk COVID-19 patients in the clinic (nirmatrelvir [Pfizer]). PBI-0451, at an appropriate dose and dosing regimen, thus has potential to provide similar clinical benefit for SARS-CoV-2-infected patients with PBI-0451.

PBI-0451 has completed toxicology studies conducted under Good Laboratory Practice guidelines, including 14-day studies in mice and dogs without evidence of adverse findings. For further information on PBI-0451, refer to the current Investigator's Brochure (IB).

1.2.2. Preclinical Pharmacology and Toxicology

PBI-0451 has shown a favorable selectivity profile at anticipated clinical exposures relative to activity against a panel of human (and rat) GPCRs, ion channels, transporters, nuclear receptors, and select enzymes (WuXi Mini Safety Panel).

For further information on PBI-0451, refer to the current IB.

1.2.3. Clinical Studies of PBI-0451

As of 1 July 2022, two clinical studies of PBI-0451 have been initiated and have completed clinical assessment: Study PBI-0451-0001 is a first-in-human, single ascending dose/multiple ascending dose study of PBI-0451 with nested food effect and drug-drug interaction (DDI) screening cohorts, and Study PBI-0451-0004 is a relative bioavailability (food effect) study.

Safety

Preliminary clinical data indicate that PBI-0451 has been well tolerated at single and multiple oral doses (ie, 10 days) up to 2100 mg/day. All reported treatment-emergent adverse events (AEs) have been mild or moderate in severity and none have been considered definitely related to study drug. No serious adverse events (SAEs) or deaths have been reported. No clinically significant treatment-emergent laboratory abnormalities, no treatment-emergent AEs due to laboratory abnormalities, and no clinically significant abnormal findings with respect to vital signs or safety electrocardiogram (ECG) assessments have been reported.

Pharmacokinetics

Preliminary clinical data demonstrate that PBI-0451 has a favorable human pharmacokinetics (PK) profile following single and multiple ascending oral doses up to 2100 mg/day. PBI-0451 demonstrates dose-linear exposures when administered with food, achieves rapid systemic

exposures that exceed the target protein-binding adjusted EC_{90} against SARS-CoV-2, and exhibits a 2-compartment PK profile that supports administration as a stand-alone agent when administered with food. PBI-0451 has been shown to be a weak CYP34A inhibitor and a nonsensitive substrate of CYP3A4, P-gp, and BCRP. DDI evaluation in vitro; in vivo; and in silico, using physiological-based PK modeling and simulation, indicated that the DDI potential of PBI-0451 as a victim or perpetrator for other major CYP enzymes and transporters is negligible. Overall, the DDI assessments suggest that PBI-0451 presents no to minimal DDI potential at the proposed clinical dose.

1.2.4. Rationale for This Study

PBI-0451 is a new chemical entity intended as an orally available DAA whose mechanism of action is inhibition of the M^{pro} of CoV, including the SARS-CoV-2 that causes COVID-19. Short-term administration (eg, 5 days) of antivirals with similar (nirmatrelvir [Pfizer]) and different (molnupiravir [Merck]) mechanisms of action have been reported to improve the outcomes (hospitalization or death) in nonhospitalized patients with SARS-CoV-2 infection at high risk for severe COVID-19. The incidence of COVID-19 remains high, mainly in unvaccinated persons, but breakthrough infections have also occurred in persons who have been fully vaccinated. PBI-0451 is an oral DAA with broad activity against CoVs, including SARS-CoV-2, and has the potential to address this unmet medical need.

1.3. Rationale for Dose Selection of PBI-0451

Dose selection for PBI-0451 included consideration of all relevant nonclinical and clinical data and knowledge from the development of DAAs used for the treatment of both acute (eg, influenza and COVID-19) and chronic (ie, HIV, hepatitis B virus (HBV), and HCV viral infections (Department of Health and Human Services 2022) (Ghany and Morgan 2020) with the goal of providing systemic drug exposures that will maximally reduce viral burden. Specifically, the goal is to achieve and maintain (accounting for protein binding) concentration multiples above the EC_{50} (US Food and Drug Administration 2006) and whenever possible also above the EC_{90} over the duration of the dosing interval.

Nonclinical and clinical data support the Phase 2 evaluation of a total daily dose of PBI-0451 1400 mg as 700 mg (2 × 350 mg tablets) BID administered with food for 5 days. This dose has been shown to achieve desired PK exposures. For additional information on PBI-0451 dose selection refer to the current IB.

Due to the desire to rapidly initiate treatment with maximally suppressive drug concentrations against SARS-CoV-2, a loading dose approach has been selected to provide the highest peak and trough PBI-0451 concentrations at the initiation of treatment (ie, Day 1), followed by the establishment of steady-state conditions for the remainder of the treatment period as described in Section 5.3). The dosing regimen is designed to assure initiation of therapy as soon as possible after randomization and administration of the full 1400 mg total daily dose on Day 1 of treatment to provide maximal antiviral activity at the point of highest viral burden and when the potential

DAA benefit is greatest. The safety of this dosing regimen is supported by single and multiple doses equal to or greater in magnitude (up to 2100 mg) and for longer duration (up to 10 days) than proposed in this Phase 2 study.

The duration of treatment in this study is 5 days, consistent with other acute antiviral treatments, such as oseltamivir for influenza. The 5-day treatment duration is identical to that shown to result in reduced rates of clinically meaningful endpoints in DAA treatment studies of COVID-19 (Jayk Bernal et al. 2022) that include SARS-CoV-2 viral load (Sasaki et al. 2022) and hospitalization due to COVID-19 or death from any cause, including nirmatrelvir (an M^{pro} inhibitor with the same mechanism of action of PBI-0451) coadministered with RTV (Hammond et al. 2022).

1.4. Risk/Benefit Assessment for the Study

No clinical safety issues specifically related to PBI-0451 have been identified to date.

The expected benefit to subjects being treated with PBI-0451 is a rapid decrease of SARS-CoV-2 viral load within a short treatment period, without the need for coadministration of a second agent for pharmacoenhancement and its potential for DDIs and potentially reduce the duration of symptomatic illness and the risk of progression to more severe disease.

Potential risks include unforeseen safety issues. For the population of subjects with SARS-CoV-2 infection, the expected benefit of eliminating SARS-CoV-2 virus within 5 days of treatment outweighs the risks associated with the possible development of previously unidentified safety issues. Subjects randomized to the placebo group may benefit from frequent medical monitoring during the study.

The overall benefit/risk balance for this study is considered favorable.

During a pandemic, additional potential risks to subjects may include interruptions to the study visit schedule and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for details on the risks and risk mitigation strategy.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
• To evaluate the antiviral activity of PBI-0451	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA)
Secondary Objectives	**Secondary Endpoint**
• To evaluate safety and tolerability of PBI-0451	• Number of treatment-emergent AEs, SAEs, discontinuation due to AEs, and Grade 3 or 4 laboratory abnormalities
• To evaluate clinical efficacy of PBI-0451 versus placebo through study Day 28	• Proportion of subjects with sustained symptom resolution through Day 28 • Time to sustained symptom resolution through Day 28 • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 • Severity of targeted COVID-19 symptoms • Number of COVID-19 related medical visits other than hospitalization, including acute/critical care visits through Day 28 • Number of days in any hospital unit for treatment of COVID-19
• To evaluate the effect of PBI-0451 on SARS-CoV-2	• Presence of SARS-CoV-2 infection based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate SARS-CoV-2 resistance to PBI-0451	• Sequence analysis of the SARS-CoV-2 M^{pro} gene (nsp5) and M^{pro} cleavage sites
• To evaluate SARs-CoV-2 resistant variant susceptibility to PBI-0451	• Susceptibility analysis of SARS-CoV-2 variants with M^{pro} amino acid substitutions and variants with

	substitutions in M^{pro} cleavage sites in the SARS-CoV-2 polyprotein
• To evaluate the relationship between SARS-CoV-2 detection methods	• Correlation of SARS-CoV-2 detection by IVA, RAT, and qRT-PCR, as specified in the CVAP
• To evaluate the incidence of rebound SARS-CoV-2 infection	• Proportion of subjects with clinical and/or virologic rebound
• To evaluate PBI-0451 PK	• PBI-0451 PK analysis from an intensive PK substudy of up to 50 subjects • PK parameters from sparse sampling of all subjects for population PK analysis

3. STUDY DESIGN

This protocol describes a Phase 2, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of PBI-0451 in nonhospitalized symptomatic adults with COVID-19 who are at standard risk of progressing to severe illness. Approximately 210 subjects will be randomized in the study.

An overview of the study design is provided in Figure 1.

3.1. Study Treatments

Following completion of screening and eligibility assessments, eligible subjects will be randomized 2:1 to 1 of 2 treatment groups on Day 1 as follows:

- PBI-0451: 2 × 350 mg tablets administered orally twice daily (BID) (1400 mg/day) with food for 5 days (10 total doses)
- Placebo: 2 × placebo to match PBI-0451 tablets administered orally BID with food for 5 days (10 total doses)

Randomization will be stratified as follows:

- SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization
- Vaccinated (ie, ≥ 1 dose of an approved vaccine) versus unvaccinated
- PK substudy participation versus nonparticipation

3.2. Duration of Treatment

Eligible subjects will begin treatment immediately following randomization and completion of Day 1 assessments (first daily dose) and with the evening meal on Day 1 (second daily dose); subjects will continue BID dosing for a total of 5 days (10 total doses).

3.3. Discontinuation Criteria

Study drug will be discontinued in the following instances:

- Unacceptable toxicity, or toxicity that, in the judgement of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Subject request to discontinue for any reason
- Pregnancy during the study (see Appendix 3)
- Concurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree

- Subject noncompliance
- Discontinuation of the study at the request of Pardes, a regulatory agency, or an institutional review board (IRB) or independent ethics committee (IEC)

Subjects who discontinue study drug are encouraged to continue participation in the study for safety follow up. Subjects can discontinue participation at any time.

3.4. End of Study

The end of this study will be the last subject's last observation (or visit) up to Week 24.

3.5. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory, specialty laboratory (for PK and/or ECG data).

3.6. Biomarker Testing Samples for Optional Future Research

The following biological specimens will be collected from all subjects who have provided consent to participate in this study, and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including AEs) and/or dosage selection, and to better understand the biological pathways, biology of SARS-CoV-2 or related diseases caused by other CoVs, and/or the validation of a companion diagnostic for COVID-19 or PBI-0451. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests that are no longer indicated and/or to add new tests based upon new state-of-the-art knowledge.

- Biological samples (blood and urine) will be collected relative to dosing (if applicable) to measure biomarkers with corresponding PK time points.
- Mid-turbinate (MT) nasal swabs will be collected to measure SARS-CoV-2 using qRT-PCR, IVA, RAT, and viral sequencing. Saliva samples will be collected to measure SARS-CoV-2 using qRT-PCR and IVA.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.

3.7. Biomarker Sample for Optional Genomic Testing

In addition to the study-specific informed consent to be signed by each subject participating in the study, subjects will be offered to document agreement to provide additional blood sample for

optional genomic research. The sample will be obtained from subjects who agree to participate and provide their additional specific consent.

A blood specimen will be collected for the evaluation of immune biomarkers that could regulate or be involved in the disposition of SARS-CoV-2 or PBI-0451. This sample will be collected at baseline/Day 1 prior to administration of the first dose of study drug but may be collected at any time during the study, if necessary.

The specimen collected for optional future genomic research may be used to advance the development of the drug and/or increase our knowledge and understanding of the biology of the disease under investigation or related diseases. This specimen may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, the specimen may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The samples collected for optional genomic research will be destroyed no later than 15 years after the end of study or per country requirements.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A total of 210 subjects will be randomized in the study. Subjects are nonhospitalized, symptomatic male and nonpregnant, nonlactating female subjects 18 to < 65 years of age with a positive direct test of SARS-CoV-2 infection (antigen based or nucleic acid amplification test [NAAT]) who are not at high-risk of progressing to severe disease.

4.1.1. Subject Replacement

Subjects who prematurely discontinue the study due to adverse events will not be replaced.

4.2. Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for participation in this study:

1. Can understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of any study procedures
2. Onset of COVID-19 symptoms ≤ 5 days prior to randomization with a positive SARS-CoV-2 test ≤ 24 hours prior to randomization. Authorized NAAT or antigen tests that detect viral RNA or protein, respectively, are allowed
3. ≥ 2 symptoms of acute COVID-19 infection as determined by the investigator from the symptoms listed on the COVID-19 symptoms questionnaire present at randomization
4. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or > 2 years post menopause
5. Male and female subjects and/or their heterosexual partners must either be of nonchildbearing potential or must use effective contraception from screening through 90 days after the last dose of study drug
6. Female subjects must refrain from egg donation and in vitro fertilization during treatment and for ≥ 28 days after the last dose of study drug
7. Male subjects must refrain from sperm donation from screening through 90 days after the last dose of study drug
8. Normal 12-lead ECG evaluation without clinically significant abnormalities
9. Able and willing to comply with all study requirements

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not eligible to participate in this study:

1. If unvaccinated, ≥ 1 Centers for Disease Control and Prevention defined underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (see Appendix 5)
2. ≥ 1 SARS-CoV-2 vaccination (including a booster) within 3 months prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period
3. Currently hospitalized or expected to require hospitalization for COVID-19 within 48 hours of randomization
4. Currently being treated or expected to be treated for COVID-19 with mAbs, convalescent serum, or DAA agents during the study period
5. Any clinical condition or laboratory result considered by the investigator to indicate any unstable or poorly controlled underlying clinically significant medical condition(s), active disseminated infection (other than SARS-CoV-2), or other medical condition that could represent a risk to the subject, including increasing the likelihood of a safety event, affect subject compliance, or affect efficacy and/or safety data collected during the 28-day study period
6. Known active liver disease, including nonalcoholic steatohepatitis/nonalcoholic fatty liver disease, chronic or active HBV or HCV infection, primary biliary cirrhosis, Child-Pugh Class B or C, chronic alcoholic liver disease, or acute liver failure
7. Receiving dialysis or having known severe renal impairment (chronic kidney disease, Stage 4 or above)
8. Unable or unwilling to comply with the protocol procedures
9. Participating in another interventional study with an investigational compound or device, including those for COVID-19
10. Known prior participation in this study or another study involving PBI-0451
11. Females who are pregnant or breastfeeding
12. Oxygen saturation of < 94% on room air

5. STUDY INTERVENTION AND CONCOMMITANT MEDICATIONS

5.1. Randomization, Blinding, and Procedures for Breaking Treatment Codes

5.1.1. Randomization

Subjects who meet eligibility criteria will be randomized in a 2:1 ratio to PBI-0451 or placebo and assigned a unique subject number via an interactive voice and web response system (IXRS) prior to initiation of dosing on Day 1. Randomization will be stratified as follows:

- SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization
- Vaccinated (ie, ≥ 1 dose of an approved vaccine) versus unvaccinated
- PK substudy participation versus nonparticipation

5.1.2. Blinding

The study is double-blinded. Subjects, investigators and all internal and external personnel directly involved in the conduct of the study will be blinded to treatment assignment. Study drug will be dispensed to subjects by the study pharmacist or designee in a blinded fashion.

Specified personnel may be unblinded based on their study role as follows:

- The statistician or designee in Biostatistics and/or Clinical Data Management who facilitates transfer of PK and/or virology sample logistics and data files between Pardes and vendors will be unblinded.
- Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Inventory Manager role in the IXRS for purpose of study drug inventory management will remain unblinded.
- Individuals in Pharmacovigilance (PVE) responsible for safety signal detection, investigational new drug (IND) safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group-level summaries.
- Individuals in Clinical Virology responsible for monitoring for virologic rebound detection will be unblinded to individual case data. In particular, RAT and qRT-PCR data will be monitored on a per subject basis to trigger the request for confirmatory sample collection in the case of a potential virologic rebound.
- External (ie, contract research organizations [CROs]) biostatisticians and programmers will be unblinded for IND safety reporting.

- A select internal team that will not participate in any other study-related activities will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will be unblinded only at the study group level and will not have access to individual subject treatment assignment.

5.1.3. Procedures for Breaking Treatment Codes

In the event of a medical emergency for which breaking the blind is required to provide medical care to a subject, the investigator may obtain treatment assignment directly from the IXRS for that subject. Pardes recommends, but does not require, that the investigator contact the CRO medical monitor prior to breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine a subject's emergency medical care. The rationale for unblinding must be clearly explained in source documentation, along with the date on which the treatment assignment was unblinded. The investigator is requested to contact the CRO medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study. Therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will discontinue study treatment. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

5.2. Description and Handling of PBI-0451

5.2.1. Formulation

PBI-0451 350 mg tablets are modified oval tablets.

Refer to latest version of the IB for additional information.

5.2.2. Packaging and Labeling

PBI-0451 tablets are packaged in 20-count high-density polyethylene bottles with silica gel desiccant(s) and labeled "For Investigational Purposes Only".

Refer to the latest version of the IB for additional information.

5.2.3. Storage and Handling

PBI-0451 should be stored at controlled room temperature (15 °C to 30 °C [59°F to 86°F]) or as otherwise labeled.

Drug product should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, drug product should not be stored in a container other than the container in which it is supplied. Consideration should be given to handling, preparation, and disposal through measures that

minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure.

A sufficient quantity of PBI-0451 (and matching placebo tables) to complete the study will be shipped to the investigator or qualified designee from Pardes or its designee.

Refer to the latest version of the IB for additional information.

5.3. Dosage and Administration

- PBI-0451: 2 × 350 mg tablets administered orally twice daily (BID) (1400 mg/day) with food for 5 days (10 total doses)
- Placebo: 2 × placebo to match PBI-0451 tablets administered orally BID with food for 5 days (10 total doses)

Subjects will take their first dose of study drug (PBI-0451 or placebo) with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1 to ensure that a full total daily dose (1400 mg PBI-0451) is taken on the first day of treatment. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of 5 days of treatment.

5.4. Prior and Concomitant Medications

Concomitant use of certain medications or herbal/natural supplements and study drug may result in PK interactions resulting in increases or decreases in exposure of study drug or the medications.

The following medications are disallowed from screening through completion of study treatment. If a subject requires use of a disallowed medication, a request for such use must be reviewed by Pardes and, if approved, the subject may continue to participate in the study.

- Any and all illegal or illicit drug use (eg, amphetamines, cocaine, opiates), including use of prescription drugs outside the care of the prescribing physician
- Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance

5.5. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug
- The date, subject number, and the study drug kit number dispensed

The date and quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Pardes recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by CRO, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to CRO.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for disposal return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability.

6. STUDY PROCEDURES

The study assessments to be conducted for each randomized subject are presented in Table 1 and described in the following sections. The investigator must document any deviation from the protocol procedures and notify Pardes and CRO.

6.1. Informed Consent

Written informed consent must be obtained from each prospective subject before initiation of any screening procedure.

6.1.1. Consent for Optional Research

Subjects who provide additional, specific consent may provide additional samples for optional biomarker research as described in Section 3.7.

6.2. Subject Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to randomization and that subjects remain eligible for the duration of the study.

Once informed consent has been obtained, all screening tests and assessments have been conducted, and study eligibility has been confirmed, a subject will be randomized to receive PBI-0451 or placebo on Day 1. Up to 50 subjects at select sites who provide separate specific consent will participate in an intensive PK substudy.

Entry into screening does not guarantee enrollment into the study. To manage the total study enrollment, Pardes, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

6.3. Pretreatment Assessments

Screening assessments may be considered as baseline/Day 1 if the subject is eligible for the study and is randomized and receives the first dose of study drug on same day.

6.3.1. Screening Visit

Prospective subjects will be screened ≤ 5 days prior to randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history
- Complete physical examination, including vital signs, body weight, and height

- Testing for SARS-CoV-2 N-antibodies using the Roche Elecsys® Anti-SARS-CoV-2 assay
- MT nasal swabs for SARS-CoV-2 RAT
- MT nasal swabs and saliva samples, as appropriate, for SARS-CoV-2 IVA, qRT-PCR, and sequence analysis
- Blood sample collection for the following analyses: hematology, chemistry, serology (HIV-1, HBV, HCV, SARS-CoV-2), serum pregnancy test (women of childbearing potential only, see Appendix 3)
- Serum/urine pregnancy test (females of childbearing potential only)
- 12-lead ECG
- Patient-reported outcomes (COVID-19 symptom questionnaire) and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility)
- Review of AEs and concomitant medication

From the time of obtaining informed consent through administration of the first dose of study drug, record all SAEs, as well as any AEs related to protocol-specified procedures on the Adverse Events electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are considered medical history (see Section 7.2).

6.3.2. Baseline/Day 1 Assessments

Note: Screening assessments may be considered as baseline/Day 1 assessments if the subject meets eligibility requirements, is randomized, and receives the first dose of study drug on same day.

The following assessments will be completed on Day 1. The investigator must have received the results from either a direct SARS-CoV-2 antigen or qRT-PCR test and results from the serum/urine pregnancy test (females of childbearing potential only) and confirmed eligibility prior to randomization. Serology tests results for HIV, HBV, HCV and SARS-CoV-2 are not required for eligibility.

At the time of randomization, subjects will be assigned a unique subject number via the IXRS. The following study assessments must be completed prior to the administration of the first dose of study drug:

- Complete physical examination, including vital signs, body weight, and height
- MT nasal swabs for SARS-CoV-2 RAT

- MT nasal swabs and saliva samples, as appropriate, for SARS-CoV-2 IVA, qRT-PCR, and sequence analysis
- Blood sample collection for the following analyses: hematology, chemistry, serology (HIV-1, HBV, HCV, SARS-CoV-2), serum pregnancy test (women of childbearing potential only, see Appendix 3)
- Creatinine clearance (CL_{CR}) (Cockcroft-Gault)
- Estimated glomerular filtration rate (eGFR, using Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2021)
- 12-lead ECG
- Biomarker sample for optional genomic testing
- Patient-reported outcomes (COVID-19 symptom questionnaire) and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) since last study visit, optional household transmission survey
- Review of AEs and concomitant medications
- Dispense study drug for all 10 doses

Subjects will take their first dose of study drug with food immediately after randomization and completion of Day 1 assessments with the second dose taken with the evening meal on Day 1. The investigator will counsel subjects as to the importance of adherence to dosing and taking study drug at approximately the same times each day (see Section 5.3).

The following Day 1 assessments will occur after the subject has taken their first dose of study drug:

- Single PK sample
- Intensive PK sampling (substudy subjects only) (Note that the intensive PK sample may be collected at any study visit from Day 1 to 5.)

6.4. Treatment Assessments

During treatment, individual study visits must occur on separate calendar days within the visit window, with the time(s) of sample collection recorded.

Study procedures and assessments during treatment Days 2 to 5 are outlined in Table 1. Symptom-driven physical examination, including vital signs; sample collection for SARS-CoV-2 RAT, qRT-PCR, and IVA; and review of AEs and concomitant medications will occur at study visits on Days 2, 3, and 5.

Assessments on Day 5 will also include a single PK sample, an evaluation of "survival status" (see Table 1), completion of the optional household transmission survey, and sample collection for SARS-CoV-2 sequence analysis (if appropriate).

6.5. Posttreatment Assessments

Posttreatment study procedures and assessments at Days 10, 15, and 28 are outlined in Table 1.

Subjects who experience a relapse in symptom(s) after having no COVID-19 symptom(s) for ≥3 days or have a positive RAT (or clinic qRT-PCR test) after testing negative by RAT or qRT-PCR will be requested to return to clinic within 2 days for MT swab and saliva samples for RAT, qRT-PCR, and sequencing.

A Week 24 follow-up assessment will be performed for all subjects (via telephone, televisit, or clinic visit, as convenient). Information regarding ongoing or recurrent COVID-19 symptoms, survival status, pregnancy status (for female subjects of childbearing potential and female partners of male subjects), and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) that have occurred since the last study visit will be collected.

6.6. Assessments for Early Discontinuation from Study

If a subject prematurely discontinues study drug, for example as a result of an AE, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures until stabilization per the investigator. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study and undergo an ET visit within 72 hours of permanently discontinuing the study drug as outlined in Table 1. Evaluations indicating abnormal results believed to be possibly or probably related to study drug at the ET visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline level, or is otherwise explained.

6.7. Pharmacokinetics Assessments

Plasma samples will be collected for measurement of PBI-0451 concentrations and estimation of PK parameters (and metabolite**[**s**]**, as applicable). Plasma collection for subjects participating in the intensive PK substudy may occur at any study visit from Day 1 (the first dose of study drug) to Day 5. Samples will be drawn at the following time points relative to PBI-0451 dosing:

Predose (≤ 5 minutes before dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and (optional) 10-12-hours postdose.

A single PK sample will be collected from all subjects at study visits at baseline/Day 1 (after the first dose of study drug) and Day 5

Any remaining PK samples will be stored in a plasma bank and may be used for exploratory assessments, such as metabolites, protein binding, endogenous markers of drug-drug interactions, biomarkers of host responsiveness, and other investigational experiments.

6.8. Safety Assessments

Safety will be evaluated throughout the study. Refer to Table 1 for the schedule of assessments. Collection of any additional assessments for routine safety monitoring at additional time points is at the discretion of the investigator based on GCP.

6.8.1. Adverse Events/Concomitant Medications/Protocol Restrictions

Evaluation for AEs, review of concomitant medications, and review of protocol restrictions will occur as outlined in Table 1. Refer to Section 7 for information regarding AEs.

Concomitant use of certain medications or herbal/natural supplements and study drug may result in PK interactions resulting in increases or decreases in exposure of study drug or the medications.

Medications that are disallowed from screening through completion of study treatment are listed below. If a subject requires use of a disallowed medication, a request for such use must be reviewed by Pardes and, if approved, the subject may continue to participate in the study.

- Any and all illegal or illicit drug use (eg, amphetamines, cocaine, opiates), including use of prescription drugs outside the care of the prescribing physician
- Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance

6.8.2. Patient-Reported Outcomes

Subjects will complete the following daily self-reported outcomes as outlined in Table 1.

- COVID-19 symptoms questionnaire
- Hospitalizations or acute/critical care visits (eg, nonadmitted hospital or other care facility) that have occurred since the last study visit

6.8.3. Household Transmission Survey

Subjects may complete the optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members as outlined in Table 1.

6.8.4. ECG assessment

ECG assessments will be conducted throughout the study as outlined in Table 1. Subjects should rest quietly in the supine position for a minimum of 5 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete.

6.8.5. Physical Examination

Complete and symptom-driven physical examinations will be conducted throughout the study as outlined in Table 1. The complete physical examination conducted at screening will include the following assessments:

- A complete physical examination must include source documentation of general appearance, and the following body systems: head, neck, thyroid; eyes, ears nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological.

- Review medical history, including history of allergies, prior and current use of nicotine or nicotine-containing products, alcohol and illegal drug use, and prior (≤ 30 days) and current medication use.

6.8.6. Vital Signs

The schedule of vital signs assessments is provided in Table 1. Vital sign measurements include blood pressure, heart rate, respiration rate, and temperature and should be taken once subjects have been seated or in the supine position for a minimum of 5 minutes. A subject's position for measurement should remain consistent throughout the study.

6.8.7. Body Mass Index

Height and weight will be collected at screening for calculation of body mass index for inclusion criteria.

6.8.8. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 1.

6.8.8.1. Blood Samples

Blood samples will be collected for the following laboratory analyses:

- Hematology: Hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume

- Coagulation panel: D-dimer, prothrombin time, activated partial thromboplastin time and international normalized ratio

- Chemistry: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, total protein, albumin, lactic acid dehydrogenase, creatine

phosphokinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (see below), glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × upper limit of normal)

- Serum pregnancy test (females of childbearing potential only)

- Serology (SARS-CoV-2 [using the Roche Elecsys® Anti-SARS-CoV-2 assay], HIV-1, HBV [hepatitis B serum antigen; hepatitis B core antibody], HCV [hepatitis C antibody, reflex to HCV RNA])

6.8.8.2. Urine Samples

Urine samples will be collected for urinalysis.

6.8.9. Creatinine Clearance and Estimated Glomerular Filtration Rate

Weight will be collected at screening to calculate CL_{CR} and eGFR.

- CL_{CR} (using the Cockcroft-Gault method based on serum creatinine and actual body weight as measured at screening):

$$\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} \left| \begin{array}{l} (\times\ 0.85 \text{ for females}) \end{array} \right| = CL_{CR} \text{ (mL/min)}$$

- eGFR (using CKD-EPI 2021) expressed as a single equation:

$$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1) \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

where:
S_{cr} = serum creatinine in mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.241 (female) or -0.302 (male)
$\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0
$\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0
Age (years)

6.9. Virology Assessments

MT nasal swab and saliva samples for virology assessment will be collected throughout the study as outlined in Table 1. The following virologic analyses are planned:

- SARS-CoV-2 IVA: $TCID_{50}$ (infected Vero E6 cell immunoassay)
- SARS-CoV-2 sequence analysis (MT nasal swab only)
- SARS-CoV-2 RAT (lateral flow immunoassay; MT nasal swab only)
- SARS-CoV-2 qRT-PCR

6.10. Sample Storage

Stored biological samples may be used by Pardes or its research partner(s) for future testing to provide additional data to answer questions that relate to the main study (refer to Section 3.6). At the end of this study, these samples may be retained in storage by Pardes for a period up to 15 years. If subjects provide additional specific consent, residual PK samples will be destroyed no later than 15 years after the end of study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a study drug that does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3). Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures, such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations in which an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-specified procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during study treatment or as a consequence of participation in the clinical study are considered AEs.

7.1.2. Serious Adverse Events

A SAE is defined as an event occurring at any time during the study that results in the following:

- Death
- A life-threatening situation (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction. Such events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, and development of drug dependency or drug abuse.

7.1.3. Study Drugs and Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the drug product, counterfeit or falsified medicine, and pregnancy, regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration, or administration of a study drug while the study drug is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a subject.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product label (as it applies to the daily dose of the subject in question). In

cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing AE relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship of an AE to a study procedure (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of the study procedure (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS Toxicity Grading Scale, Version 2.1. For each episode, the highest grade attained should be reported as defined in the grading scale (Appendix 4).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-specified procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship to study drug, until Day 28, and report them on the eCRFs as instructed.

All AEs should be followed until resolution or until the AE is stable, if possible. Pardes may request that certain AEs be followed beyond the protocol-specified follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship to study drug or a protocol-specified procedure, that occur after a subject consents to participate in the study (ie, after signing the ICF) through study Day 28, must be reported on the applicable eCRFs and to the CRO PVE as instructed below in this section.

Any SAEs and deaths that occur after Day 28, regardless of causality, should also be reported.

PPD NA PVE
Phone: +1 888 483 7729
Fax: +1 888 529 3580

Investigators are not obligated to actively seek SAEs after study Day 28; however, if the investigator learns of any SAEs that occur after Day 28, and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to CRO PVE.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug special situations that occur from study drug initiation through study Day 28 must be reported to CRO PVE (Section 7.4.2). AEs and SAEs resulting in SSRs must be reported in accordance with the AE and SAE reporting guidance.

7.3.5. Concomitant Therapy Reports

7.3.5.1. Concomitant Therapy Special Situations Report

SSRs involving a concomitant therapy (not considered study drug) that occur after the subject first consents to participate in the study (ie, after signing the ICF) through study Day 28, must be reported to CRO PVE utilizing the paper SSR (Section 7.4.2.3).

7.3.5.2. Concomitant Therapy Report

Special situations involving concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the subject's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and transmit the SAE information to CRO PVE within 24 hours of the investigator's knowledge of the event from ICF signature through study Day 28.

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit to CRO PVE within 24 hours:

PPD NA PVE
Phone: +1 888 483 7729
Fax: +1 888 529 3580

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to CRO PVE.

7.4.1.2. Paper Serious Adverse Event Reporting Process

- All SAEs will be recorded on the SAE report form and transmitted by email or fax within 24 hours of the investigator's knowledge of the event to the attention of CRO PVE from ICF signature through study Day 28.

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Fax: +1 888 529 3580

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

- Site personnel will record all special situation data on the applicable eCRFs and transmit the information to CRO PVE from study drug initiation through study Day 28.

- If for any reason it is not possible to record the special situation information electronically, record the special situation on the paper SSR form and transmit to CRO PVE:

PPD NA PVE
Phone: +1 888 483 7729
Fax: +1 888 529 3580

- If a special situation has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any special situation reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to CRO PVE.

- See Section 7.4.2.3 for instructions on reporting special situations with concomitant medications.

7.4.2.2. Paper Special Situations Reporting Process for Study Drug

- All special situations will be recorded on the SSR form and transmitted by email or fax within 24 hours of the investigator's knowledge of the event to the CRO PVE from study drug initiation through Day 28.

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Fax: +1 888 529 3580

7.4.2.3. Reporting Process for Concomitant Medications

- Special situations that involve concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to CRO PVE utilizing the paper SSR form to:

PPD NA PVE Phone: +1 888 483 7729
Fax: +1 888 529 3580

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

- Special situations involving concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a concomitant medication, must be reported as AEs.

7.4.2.4. Pregnancy Reporting Process

- The investigator should report pregnancies in female study subjects and/or female partners of male subjects that are identified after initiation of study drug and throughout the study, including the posttreatment follow-up period, to CRO PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

PPD NA PVE Phone: +1 888 483 7729
Fax: +1 888 529 3580

- The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

- Any other premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to the CRO PVE.

- The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to CRO PVE using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to CRO PVE.

PPD NA PVE	Phone: +1 888 483 7729
	Fax: +1 888 529 3580

- Refer to Appendix 3 for pregnancy precautions, definition of female of childbearing potential, and contraceptive requirements.

7.5. Sponsor Reporting Requirements

Depending on relevant local legislation and regulations, including the applicable FDA Code of Federal Regulations, the European Union Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation and regulations, Pardes may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions, or SUSARs. In accordance with the European Union Clinical Trials Directive (2001/20/EC), Pardes or a specified designee will notify worldwide regulatory agencies and the relevant IEC(s) in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by CRO PVE using reference safety information specified in the IB or relevant local label, as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as AEs or SAEs as applicable. In addition, laboratory or other abnormal assessments (eg, ECGs, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a

syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Division of AIDS Toxicity Grading Scale, Version 2.1 (Appendix 4). AEs associated with laboratory abnormalities should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the CRO medical monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Severity of AEs should be recorded and graded according to the following:

- Grade 1 (Mild) clinical AE defined as mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated will continue with study participation.
- Grade 2 (Moderate) clinical AE defined as moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated will continue with study participation if interventions are not contraindicated and the investigator and medical monitor agree to continue.
- Grade 3 (Severe) clinical AEs defined as severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated will discontinue study drug administration and continue with study follow-up assessments.
- Grade 4 (Potentially Life-Threatening) clinical AEs are defined as potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability; and will discontinue study participation.
- Grade 5 indicates death.

Any questions regarding toxicity management should be directed to the CRO medical monitor.

8. STATISTICAL CONSIDERATIONS

Summary statistics will be used to analyze the study data. Any statistical testing will be conducted to ensure that the overall alpha = 0.05 level (2 sided). Unless otherwise specified, data summaries and analyses will be reported by treatment group. Details of the statistical methods will be provided in the statistical analysis plan (SAP), including any deviations from the original planned analyses.

8.1. Analysis Objectives and Endpoints

The primary, secondary, and exploratory study objectives and endpoints are listed in Section 2.

8.2. Planned Analysis

8.2.1. Interim Analysis

An analysis of the primary and secondary endpoints will be conducted after 210 subjects complete the Day 28 study visit.

8.2.2. Final Analysis

The final analysis will be conducted after the last randomized subject has completed their Week 24 follow-up visit or discontinued the study, all outstanding data queries have been resolved, and the database has been cleaned and locked.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Enrolled Analysis Set

The all enrolled analysis set includes all subjects who sign the ICF. This is the primary analysis set for disposition.

8.3.1.2. Intention-to-Treat Analysis Set

The intention-to-treat (ITT) analysis set includes all randomized subjects. This is the primary analysis set for demographics and data listings.

8.3.1.3. Modified Intention to Treat Analysis Set

The modified intention-to-treat (mITT) analysis set includes all randomized subjects with ≥ 2 symptoms consistent with COVID-19 ≤ 5 days prior to randomization and a positive SARS-CoV-2 test (RT-PCR or RAT) ≤ 24 hours prior to randomization who received ≥ 1 dose of study drug. This is the primary analysis set for all clinical endpoints.

8.3.1.4. Modified Intent to Treat Virologic Analysis Set

The mITT virologic analysis set is a subset of the mITT analysis set that includes subjects who had detectable infectious SARS-CoV-2 at baseline/Day 1. This is the primary analysis set for the primary efficacy endpoint.

8.3.1.5. Safety Analysis Set

The safety analysis set includes all randomized subjects who received ≥ 1 dose of study drug. This is the primary analysis set for safety analyses.

8.3.1.6. Pharmacokinetics Analysis Set

The PK analysis set includes all subjects who participated in the intensive PK substudy and have ≥ 1 nonmissing PK concentration reported by the PK laboratory. This is the primary analysis set for PK analyses

8.3.2. Data Handling Conventions

8.3.2.1. Missing Data

Missing data can have an impact upon the interpretation of the study data. As this study is of short duration, it is anticipated that missing data will be minimal. Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled. Any imputations of missing data will be described in the SAP.

8.3.2.2. Adjustments for Multiplicity

No adjustments for multiplicity are planned.

8.4. Demographic and Baseline/Day 1 Characteristics Analysis

Demographics (age, gender, race/ethnicity), and subject characteristics (SARS-CoV-2 Pango lineage, SARS-CoV-2 seropositivity, qRT-PCR, time since onset of symptoms) will be summarized by treatment group using descriptive statistics for the ITT analysis set.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of subjects below the LOD for infectious SARS-CoV-2 on Day 3 by IVA. For the primary endpoint, differences between PBI-0451 and placebo will be evaluated using stratum-adjusted Mantel-Haenszel proportions (adjusted for randomization strata). The proportion of subjects below the LOD for infectious SARS-CoV-2 at other time points will be summarized in a similar manner.

8.5.2. Secondary Analyses

The time to resolution of targeted COVID-19 symptoms will be estimated with the Kaplan-Meier method and summarized by treatment group. Differences between treatment groups will be determined using a Wilcoxon-Gehan test. The analysis of time to resolution of each targeted COVID-19 symptom will be conducted in a similar manner.

The proportion of subjects with COVID-19 related hospitalization or death from any cause will be summarized by treatment group. Differences between treatment groups will be assessed using Mantel-Haenszel proportions.

The number of COVID-19 related hospitalizations or acute/critical care visits and the number of days in any hospital unit for the treatment of COVID-19 will be summarized. Differences between treatment groups will be assessed using a van Elteren test stratified by the randomization factors.

SARS-CoV-2 viral load kinetics will be summarized by study visit. Differences between the treatment groups will be assessed with a van Elteren test stratified by the randomization factors.

SARS-CoV-2 clinical and virologic rebound will be summarized by the amount of viral RNA detected at baseline/Day 1, time to loss of clinical symptoms, time to negative RAT or IVA, and time to the first confirmed reappearance of symptoms and/or a positive RAT or qRT-PCR sample.

A correlation of the results of IVA, RAT, and qRT-PCR assessments will be evaluated.

8.6. Safety Analysis

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be determined from the study drug administration data. Exposure data will be summarized using descriptive statistics and listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. A treatment-emergent AE is defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 14 days. Treatment-emergent AEs, SAEs, and AEs leading to premature discontinuation of study drug/study will be summarized by treatment, system organ class, and preferred term.

Laboratory results and change from predose values for selected laboratory tests will be summarized by treatment at scheduled visits. The incidence of treatment-emergent laboratory abnormalities (Division of AIDS Toxicity Grading Scale) will be summarized by treatment.

By-subject listings of safety data will be provided.

8.6.3. Laboratory Evaluations

Listings of individual subject laboratory results will be provided. Selected laboratory data will be summarized using only observed data. Data and change from baseline/Day 1 at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined in the SAP. Incidence of treatment-emergent laboratory abnormalities, defined as values that increase ≥ 1 toxicity grade from baseline/Day 1 at any postbaseline time point up to and including the date of last dose of study drug plus 14 days will be summarized by treatment group. If baseline/Day 1 data are missing, any graded abnormality (ie, ≥ Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has discontinued study drug for ≥ 14 days will be listed.

8.6.4. Other Safety Evaluations

Vital signs and (safety) ECG data will be listed.

8.7. Pharmacokinetics Analysis

PBI-0451 plasma concentrations and PK parameters will be derived using noncompartmental methods (including metabolite[s] as applicable) and listed and summarized using descriptive statistics.

PBI-0451 plasma concentrations from the PK substudy and sparse sampling from the overall study population will be used in a population PK analysis and reported separately.

8.8. Sample Size

The sample size will be approximately 210 subjects to account for approximately 60% of randomized subjects who are anticipated to be SARS-CoV-2 negative by IVA at baseline/Day 1 and would be excluded from the mITT virologic analysis set. It should be noted that this sample size is sufficient with ≥ 80 power to detect a > 19% absolute difference in the proportion of subjects below the LOD for infectious SARS-CoV-2 virus (99% vs 81%) at Day 3 by IVA among subjects who had detectable infectious SARS-CoV-2 at baseline/Day 1. This assumes alpha = 0.05 and that 40% of subjects have detectable infectious virus at baseline/Day 1.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Pardes or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Pardes or CRO of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or designated personnel as appropriate according to local regulations) will submit this protocol, the ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements).

The ICF will inform subjects about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. In addition to the study specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples for optional genomic research. The results of the tests done on the samples will not be given to the subject or the investigator.

9.1.5. Confidentiality

The investigator must ensure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Pardes, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions in accordance with local regulations. NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Pardes or its partner(s), including but not limited to the IB, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Pardes during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Pardes. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, IEC and government approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification
- Documentation that subject meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis) to support inclusion and exclusion criteria
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation if it occurs

All clinical study documents must be retained by the investigator for ≥ 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Pardes. The investigator must notify Pardes before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Pardes must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Pardes to store these records securely away from the site so that they can be returned sealed to the investigator

in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will capture only the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines (CCGs). Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or CRO staff who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries, as well as any changes to data fields, will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by CRO), the investigator will use his/her login credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, CRO will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to CRO's appointed study monitors, IRBs/IECs, and regulatory or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Pardes. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. Pardes will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Pardes in an abstract, manuscript, or presentation form or the study has been completed at all study sites for ≥ 2 years.
- The investigator will submit to Pardes any proposed publication or presentation along with the respective scientific journal or presentation forum ≤ 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Pardes's confidential information (see Section 9.1.5).
- The investigator will comply with Pardes's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Pardes will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Pardes/CRO may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the CRO medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Pardes/CRO access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Pardes and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority, and IRB/IEC. In terminating the study, Pardes/CRO and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

PARDES BIOSCIENCES, INC.
2173 SALK AVE SUITE 250
PMB #052
CARLSBAD, CA 92008

STUDY ACKNOWLEDGMENT

A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19

Original

07 July 2022

This protocol has been approved by Pardes Biosciences, Inc. The following signature documents this approval.

Brian Kearney, PharmD

Name (Printed)
Chief Development Officer

DocuSigned by:
Brian P. Kearney
Signature
Signer Name: Brian P. Kearney
Signing Reason: I approve this document
Signing Time: 7/8/2022 | 12:24:25 AM PDT
866517FE3DE7400BB6328B087659F93C

7/8/2022

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein, and I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Pardes or its partner(s). I will discuss this material with them to ensure that they are fully informed about the drugs, the study, and the undertaking of confidentiality.

I agree that all information received from Pardes or its partner(s), including but not limited to the Investigator's Brochure, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Pardes during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written

consent from Pardes. I further agree to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2 Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to subjects and sites:

    a) Subjects may be unable to return to the site to get the study drug, or the site may be unable to accept any subject visits. Without study drug, a subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: Study drug supplies may be provided to the subject from the site without a clinic visit, once it is confirmed that the subject may safely continue on study drug as determined by the investigator. A virtual study visit, via telephone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person subject visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study subjects if permitted by local institutional review board (IRB)/ independent ethics committee (IEC) as applicable and with Pardes's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug, a subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify Pardes or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. Pardes will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

2) Subject safety monitoring and follow-up:

    a) Subjects may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

        Mitigation plan: For subjects who may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol, the Investigator or qualified delegate will conduct a virtual study visit, via telephone or video conferencing, to assess the subject within the target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

        i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

iv) If applicable, confirm subjects study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in Item 1 above.

v) If applicable, remind subject to maintain current dosing and to keep all dispensed study drug kits for return at the next onsite visit.

b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories may be used as appropriate to monitor subject safety until the subject can return to the site for their scheduled visit per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local IRB/IEC and national laws and regulations. Remote consent will be allowed if has been approved by the local IRB/IEC. The consent process will be documented and confirmed by the normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur if scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required scheduled procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed subject visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification (SDV) or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or under-reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. In compliance with CRO policy, a remote SDV should not be arranged). The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to subjects missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of PBI-0451 in study subjects remains unchanged.

Appendix 3 Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the subject is permanently sterile or has medically documented ovarian failure.

Females are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless the subject is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

PBI-0451 is contraindicated in pregnancy because a malformation effect is unknown, taking into consideration class effects and genotoxic potential. PBI-0451 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, as there is limited safety information available to exclude the possibility of DDIs between PBI-0451 and hormonal contraception, hormonal contraception methods are not an acceptable form of contraception for female subject participating in this study. Female subjects must use one of the highly effective contraceptive methods outlined below in Section 2.b.

Refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must also not rely on hormonal contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative pregnancy test on Day 1 prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter until the end of the contraception requirement.

Duration of required contraception for female subjects in this study is from screening and until 90 days after the last dose of study drug. Female subjects must agree to one of the following contraceptive methods:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of ≥ 1 of the following methods of birth control:
  - Nonhormonal intrauterine device (IUD)
  - Bilateral tubal occlusion (upon medical assessment of surgical success)
  - Vasectomy in the male partner (upon medical assessment of surgical success)
  - Consistent and correct use of a double barrier method of contraception using two of the following barriers concurrently:
    - Male condoms
    - Female condoms
    - Female diaphragm ('cap')

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved. Local requirements of combining a single barrier method with either IUD or surgical sterilization are endorsed.

Female subjects must refrain from egg donation and in vitro fertilization during treatment and for ≥ 28 days after the last dose of study drug.

3) Contraception Requirements for Male Subjects

Male subjects must agree to use a male condom and an additional effective contraceptive method with their female partners, if their female partners are of childbearing potential (see Section 1.a), from treatment Day 1 until 90 days following the last dose of study drug. Effective methods of contraception for female partners of male subjects may include hormonal contraception or one of the methods outlined in Section 2.b.

Male subjects must refrain from sperm donation from screening throughout the study period and for at least 90 days following the last dose of study drug.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from screening to 90 days after the last dose of study drug. Study drug must be discontinued immediately if pregnancy is confirmed during treatment.

Male subjects whose partner has become pregnant or suspects she is pregnant from screening to 90 days after the last dose of study drug must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.4.

Appendix 4 Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Please refer to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1 – July 2017)

Appendix 5 Modified Centers for Disease Control and Prevention: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19

At least 1 underlying medical condition associated with increased risk for severe COVID-19 illness ("high-risk" and consequently increased risk of hospitalization and death). Applicable comorbidities are to be derived from the Centers for Disease Control and Prevention list of high-risk underlying conditions as outlined below and detailed at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

a. ≥65 years of age
b. Asthma
c. Active cancer
d. Cerebrovascular disease
e. Chronic kidney disease (if no history of CKD Stage 3 or above)
f. Chronic lung diseases limited to:
    i. Interstitial lung disease
    ii. Pulmonary embolism
    iii. Pulmonary hypertension
    iv. Bronchiectasis
    v. COPD (chronic obstructive pulmonary disorder)
g. Chronic liver diseases limited to:
    i. Cirrhosis (Child-Pugh A)
    ii. Non-alcoholic fatty liver disease
    iii. Alcoholic liver disease
    iv. Autoimmune hepatitis
h. Cystic fibrosis
i. Diabetes mellitus, Type 1 and Type 2
j. Disabilities

i. Attention-Deficit/Hyperactivity Disorder (ADHD)

ii. Cerebral Palsy

iii. Congenital Malformations (Birth Defects)

iv. Limitations with self-care or activities of daily living

v. Intellectual and Developmental Disabilities

vi. Learning Disabilities

vii. Spinal Cord Injuries

k. Heart conditions such as:

i. heart failure

ii. Coronary artery disease

iii. Cardiomyopathies

l. HIV (human immunodeficiency virus)

m. Mental health disorders limited to:

i. Mood disorders, including depression

ii. Schizophrenia spectrum disorder

n. Neurological conditions limited to dementia

o. Obesity (BMI $\geq$30 kg/m^2)

p. Primary Immunodeficiencies

q. Solid organ or blood stem cell transplantation

r. Tuberculosis

s. Use of corticosteroids or other immunosuppressive medications

t. Immune deficiencies (except people with moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments)

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SUMMARY OF CHANGES

PBI-0451-0002

A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19

The following summary of changes outline the rationale for the changes made from the prior version of the study protocol to the current version of the study protocol	Original, 07 July 2022
	Amendment 1, 26 August 2022

General:	Administrative corrections to spelling, grammar, formatting, version updates, pagination, and cross-references are not itemized.

Section and page	Synopsis, Primary Endpoint, page 7
Original Text	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA)
New Text	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA) from mid-turbinate (MT) swabs
Rationale for Change	Detail of swab method requested by FDA.

Section and page	Synopsis, Secondary Endpoint, page 8
Original Text	• Presence of SARS-CoV-2 infection based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)

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New Text	• Presence of SARS-CoV-2 virus, viral RNA or viral antigen based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)
Rationale for Change	Detail of IVA methodology requested by FDA.

Section and page	Synopsis, Inclusion Criteria, Page 9
Original Text	*New Text Inserted* *AND* 4. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or >2 years postmenopause.
New Text	3. Received primary vaccination series as defined by Centers for Disease Control and Prevention (CDC). (Subjects should be advised during informed consent that alternate therapies may be available outside of study participation.) AND 5. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or in a postmenopausal state.
Rationale for Change	Clarified subjects must meet minimum vaccination standards to participate and must be informed of alternate therapies at request of Advarra IRB. Numbered items formatted. Criteria 5 aligned with Appendix 3 of protocol and referenced, for clarity and consistency.

Section and page	Synopsis, Exclusion Criteria, Page 10-11
Original Text	10. If unvaccinated, ≥1 Centers for Disease Control and Prevention defined underlying medical condition associated with an increased risk of developing severe illness from COVID-19. AND *New Text Inserted* AND 11. ≥1 SARS-CoV-2 vaccination (including a booster) within 3 months prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period AND

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	13. Currently begin treated or expected to be treated for COVID-19 with monoclonal antibodies, convalescent serum, or direct-acting antiviral agents
New Text	1. Considered at high-risk of developing severe illness from COVID-19 defined as ≥1 CDC underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (see Appendix 5) AND 2. Unvaccinated against SARS-CoV-2 (defined as having not completed a primary vaccination series) AND 3. Any SARS-CoV-2 vaccination within 3 months prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period AND 5. Currently begin treated or expected to be treated for COVID-19 with monoclonal antibodies, convalescent serum, or direct-acting antiviral agents (all potential subjects should be informed of evolving treatment options during informed consent that alternate therapies may or may not be available to them outside of study participation)
Rationale for Change	Formatted numbering. Excluded unvaccinated subjects from study participation at request of Advarra IRB. Clarified exclusion of subjects who have at least one CDC defined risk factor for developing severe COVID-19 illness (listed in Appendix 5) and by denoting that if subjects have begun treatment or expect to begin treatment of listed products, then they meet definition of high-risk and must be excluded. All subjects (qualified or not) should be informed of available COVID-19 treatment options to reduce risk of severe COVID-19 disease progression.

Section and page	Synopsis, Study Procedures/Frequency, Page 11
Original Text	Randomization will be stratified as follows: • SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization • Vaccinated (ie, ≥1 dose of an approved vaccine) versus unvaccinated • PK substudy participation versus nonparticipation
New Text	Randomization will be stratified as follows: • SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization • Received primary vaccination series, alone versus any booster shots • PK substudy participation versus nonparticipation

Rationale for Change	Unvaccinated subjects excluded from participation at request of Advarra IRB. Stratification will now include subjects who have received primary vaccination only versus subjects who have a least one COVID-19 booster.

Section and page	Synopsis, Patient Reported Outcomes, Page 11
Original Text	• COVID-19 symptom questionnaire • COVD-19 related hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) since the last study visit Hospitalization is defined as > 24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19. This includes any special medical care unit within an assisted living facility or nursing home. • Optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members (baseline/Day 1 and Days 5, 10, 15, and 28 or ET only)
New Text	• COVID-19 symptom questionnaire • COVID-19 weekly questionnaire • COVD-19 related hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) since the last study visit Hospitalization is defined as > 24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19. This includes any special medical care unit within an assisted living facility or nursing home. • Optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members (baseline/Day 1 and Days 5, 10, 15, 28 or ET only, and rebound ad hoc visit (if applicable))
Rationale for Change	Weekly COVID-19 questionnaire added at request of FDA. Optional household transmission survey added to rebound ad hoc visit added to enhance rebound or re-infection ad hoc analysis.

Section and page	Synopsis, Serology Testing AND Virologic Assessments, Page 12
Original Text	**Serology Testing:** Serology samples at screening and/or baseline/Day 1 AND • SARS-CoV-2 (using the Roche Elecsys® Anti-SARS-CoV-2 assay) AND

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	Virologic Assessments: The following tests will be performed from mid-turbinate (MT) nasal swab and saliva samples at screening, baseline/Day 1, and Days 2, 3, 5, 10, 15, 28 or early termination (ET) AND • SARS-CoV-2 IVA (MT swab and saliva) at baseline/Day 1 and Days 2, 3, 5, and 10, only • SARS-CoV-2 sequence analysis (MT swab) at baseline/Day 1 and Day 5 for all subjects to evaluate the potential for the development of resistance in response to treatment with PBI-0451. Additional time points may be evaluated in the case of virologic rebound or if the subject remains viremic at other study visits through Day 28 (ie, if SARS-CoV-2 RNA by qRT-PCR is ≥ 3.85 $\log_{10}$ copies/mL, which is the threshold for the minimum amount of viral RNA required for whole genome sequencing).
New Text	**Serology Testing:** Serology samples at screening and/or baseline/Day 1 AND • SARS-CoV-2 N-antibodies (using the Roche Elecsys® Anti-SARS-CoV-2 assay) AND **Virologic Assessments**: The following tests will be performed from mid-turbinate (MT) nasal swab and saliva samples at screening, baseline/Day 1, and Days 2, 3, 5, 10, 15, 28 or early termination (ET), and rebound ad hoc visit (if applicable) AND • SARS-CoV-2 IVA (MT swab and saliva) at baseline/Day 1 and Days 2, 3, 5, 10, Day 15, rebound and early termination SARS-CoV-2 sequence analysis (MT swab) at baseline/Day 1 and Day 5 for all subjects to evaluate the potential for the development of resistance in response to treatment with PBI-0451. Additional time points may be evaluated in the case of virologic rebound or if the subject remains viremic at other study visits (ie, if SARS-CoV-2 RNA by qRT-PCR is ≥ 3.85 $\log_{10}$ copies/mL, which is the threshold for the minimum amount of viral RNA required for whole genome sequencing).
Rationale for Change	Additional detail of SARS-CoV-2 antibody test and additional timepoints added at rebound and/or beyond Day 10 at request of FDA.

Section and page	Synopsis, Safety Assessments AND Medical Monitoring AND Rescue Therapy, Page 12-13
Original Text	**Safety Assessments:** AND • Vital signs: All visits AND *New Text Inserted*

New Text	**Safety Assessments:** AND • Vital signs: All visits through Day 28 AND **Medical Monitoring** A team of medically qualified individuals, including but not limited to, the Sponsor and the CRO Medical Monitors, and the Drug Safety Consultant are responsible for ongoing review of all AEs, concomitant medications, laboratory values (including virology), and vital signs (including pulse oximetry), worsening of symptoms (COVID-19 symptom questionnaire, including dyspnea), acute/critical care visits (eg, nonadmitted hospital or other care facility), and study drug discontinuations, at a minimum monthly basis throughout the study, per the Safety Monitoring Plan. Serious adverse events (eg, hospitalizations, life threatening events, medically important events, deaths) will be evaluated by the Sponsor and the CRO Medical Monitor within 24 hours after being reported by the Investigator. Blinded study data will be evaluated for trends and any event which occurs in greater frequency will be evaluated for updating risk language and notifying the IRB and regulatory authorities, as required. **Rescue Therapy** Subjects who experience severe COVID-19 illness (defined in this study as sustained pulse oximetry <94%, a respiratory rate of >30 breaths/min, or dyspnea that requires medical attention) should discontinue study drug and be immediately referred by the Investigator to emergency care or treated by the Investigator for standard of care treatment of symptoms including, but not limited to, other antivirals, supplemental oxygen, corticosteroids, Janus kinase inhibitors, or interleukin-6 blockers, in accordance with the NIH Treatment Guidelines (NIH 2022). The subject should continue participation in the study, with study drug discontinued, for safety follow-up and clinical outcome of the medically attended visit.
Rationale for Change	Clarified vital signs assessed at all visits through Day 28. Medical Monitoring and Rescue Therapy details provided at request of Advarra IRB to ensure subject safety through study conduct.

Section and page	Table 1. Study Procedures Table, Page 17-19
Original Text	Table updated to reflect changes in body of text.
New Text	
Rationale for Change	Updates to table made based on requests from FDA, Advarra IRB, and administrative clarifications.

Section and page	Section 1.4. Risk/Benefit Assessment for the Study, Page 24
Original Text	No clinical safety issues specifically related to PBI-0451 have been identified to date.

	The expected benefit to subjects being treated with PBI-0451 is a rapid decrease of SARS-CoV-2 viral load within a short treatment period, without the need for coadministration of a second agent for pharmacoenhancement and its potential for DDIs and potentially reduce the duration of symptomatic illness and the risk of progression to more severe disease. Potential risks include unforeseen safety issues. For the population of subjects with SARS-CoV-2 infection, the expected benefit of eliminating SARS-CoV-2 virus within 5 days of treatment outweighs the risks associated with the possible development of previously unidentified safety issues. Subjects randomized to the placebo group may benefit from frequent medical monitoring during the study. The overall benefit/risk balance for this study is considered favorable. During a pandemic, additional potential risks to subjects may include interruptions to the study visit schedule and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for details on the risks and risk mitigation strategy.
New Text	The overall benefit/risk balance for this study is considered favorable. The target patient population under study for this protocol is designed to exclude patients who are at high risk of progression to severe COVID-19 and thus for which there may be no approved or authorized treatments. During a pandemic, additional potential risks to subjects may include interruptions to the study visit schedule and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for details on the risks and risk mitigation strategy
Rationale for Change	Section 1.4.1, Risk/Benefit for PBI-0451; Section 1.4.2, Risk/Benefit for Placebo; and Section 1.4.3, Potential Alternatives to Placebo added to provide more guidance and detail to Investigators at the request of Advarra IRB.

Section and page	Section 1.4.1. Risk/Benefit for PBI-0451, Page 24
Original Text	*New Text Inserted*
New Text	No clinical safety issues specifically related to PBI-0451 have been identified to date. The expected benefit to subjects being treated with PBI-0451 is a rapid decrease of SARS-CoV-2 viral load within a short treatment period, without the need for coadministration of a second agent for pharmacoenhancement and its potential for DDIs and potentially reduce the duration of symptomatic illness and the risk of progression to more severe disease. Potential risks include unforeseen safety issues, the lack of efficacy and the risk of progression to more severe COVID-19 disease progression. For the population of subjects with SARS-CoV-2 infection, the expected benefit of eliminating SARS-

	CoV-2 virus within 5 days of treatment outweighs the risks associated with the possible development of previously unidentified safety issues.
Rationale for Change	Section 1.4.1, Risk/Benefit for PBI-0451; Section 1.4.2, Risk/Benefit for Placebo; and Section 1.4.3, Potential Alternatives to Placebo added to provide more guidance and detail to Investigators at the request of Advarra IRB.

Section and page	Section 1.4.2. Risk/Benefit for Placebo, Page 24
Original Text	*New Text Inserted*
New Text	Subjects randomized to the placebo group may benefit from frequent medical monitoring during the study as there is a potential risk of severe COVID-19 disease progression
Rationale for Change	Section 1.4.1, Risk/Benefit for PBI-0451; Section 1.4.2, Risk/Benefit for Placebo; and Section 1.4.3, Potential Alternatives to Placebo added to provide more guidance and detail to Investigators at the request of Advarra IRB.

Section and page	Section 1.4.3. Potential Alternatives to Placebo, Page 25
Original Text	*New Text Inserted*
New Text	Investigators should review all available treatment options for each individual subject, including those outside of this study, and risks associated with placebo with the potential subject. The Investigator should refer to the "NIH Treatment Guidelines" (NIH 2022), and the CDC "Interim Clinical Considerations for COVID-19 Treatment in Outpatients" and "Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals" to appropriately discuss the alternative options and risks for being in this study (CDC 2022). The potential participant should also be referred to or receive a printout of the CDC "People with Certain Medical Conditions" and "COVID-19 Treatments and Medications" which includes language appropriate for the lay person regarding medical conditions attributed to a higher risk of severe COVID-19 and potential treatment (CDC 2022). 1. The following products are either FDA approved or authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and are recommended as first line agents by the NIH Treatment Guidelines: • Veklury (remdesivir) – FDA approved (Gilead Sciences 2022)

	• Paxlovid (nirmatrelvir) boosted with ritonavir – Emergency Use Authorization (US Food and Drug Administration 2022c) 2. The following products have emergency use authorization by the FDA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are high risk for progression to severe COVID-19, including hospitalization or death, **and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate** per the NIH Treatment Guidelines. • Lagevrio (molnupiravir) – Emergency Use Authorization (US Food and Drug Administration 2022a) • Bebtelovimab – Emergency Use Authorization (US Food and Drug Administration 2022b) 3. The list of approved or authorized products is subject to change during the course of the study, the complete list of FDA products can be found here: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs and the NIH Treatment Guidelines can be found here; https://www.covid19treatmentguidelines.nih.gov/
Rationale for Change	Section 1.4.1, Risk/Benefit for PBI-0451; Section 1.4.2, Risk/Benefit for Placebo; and Section 1.4.3, Potential Alternatives to Placebo added to provide more guidance and detail to Investigators at the request of Advarra IRB.

Section and page	Section 2. OBJECTIVES AND ENDPOINTS, Page 27
Original Text	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA) AND • Presence of SARS-CoV-2 infection based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)
New Text	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA) from mid-turbinate (MT) swabs AND • Presence of SARS-CoV-2 virus, viral RNA, or viral antigen based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR),

	and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)
Rationale for Change	Detail of swab method and detail of IVA methodology requested by FDA.

Section and page	Section 3.1. Study Treatments, Page 29
Original Text	Randomization will be stratified as follows: • SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization • Vaccinated (ie, ≥1 dose of an approved vaccine) versus unvaccinated • PK substudy participation versus nonparticipation
New Text	Randomization will be stratified as follows: • SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization • Received primary vaccination series, alone versus any booster shots • PK substudy participation versus nonparticipation
Rationale for Change	Unvaccinated subjects excluded from participation at request of Advarra IRB. Stratification will now include subjects who have received primary vaccination only versus subjects who have a least one COVID-19 booster.

Section and page	Section 3.3. Discontinuation Criteria, Page 30
Original Text	*New Text Inserted*
New Text	• Subjects develop severe or critical COVID-19 illness defined as sustained pulse oximetry <94%, a respiratory rate of >30 breaths/min or dyspnea that requires medical attention
Rationale for Change	Specific stopping rules for subjects who develop severe COVID-19 illness added at the request of Advarra IRB.

Section and page	Section 3.3.1. Rescue Therapy for Discontinuation, Page 30
Original Text	*New Text Inserted*
New Text	Subjects who experience severe COVID-19 illness (defined in this study as sustained pulse oximetry <94%, a respiratory rate of >30 breaths/min, or dyspnea that requires medical attention) should discontinue study drug and be immediately referred by the Investigator to emergency care or treated by the Investigator for standard of care

	treatment of symptoms including, but not limited to, other antivirals, supplemental oxygen, corticosteroids, Janus kinase inhibitors, or interleukin-6 blockers, in accordance with the NIH Treatment Guidelines (NIH 2022). The subject should continue participation in the study, with study drug discontinued, for safety follow-up and clinical outcome of the medically attended visit
Rationale for Change	Specific guidance for rescue therapy during study conduct for subjects who experience severe COVID-19 illness added at the request of Advarra IRB.

Section and page	Section 4.2. Inclusion Criteria, Page 32
Original Text	*New Text Inserted* *AND* 4. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or >2 years postmenopause.
New Text	3. Received primary vaccination series as defined by Centers for Disease Control and Prevention (CDC). (Subjects should be advised during informed consent that alternate therapies may be available outside of study participation.) AND 5. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or in a postmenopausal state.
Rationale for Change	Clarified subjects must meet minimum vaccination standards to participate and must be informed of alternate therapies at request of Advarra IRB. Numbered items formatted. Criteria 5 aligned with Appendix 3 of protocol and referenced, for clarity and consistency.

Section and page	Section 4.3. Inclusion Criteria, Page 33
Original Text	10. If unvaccinated, ≥1 Centers for Disease Control and Prevention defined underlying medical condition associated with an increased risk of developing severe illness from COVID-19. AND *New Text Inserted* AND 11. ≥1 SARS-CoV-2 vaccination (including a booster) within 3 months prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period

	AND 13. Currently begin treated or expected to be treated for COVID-19 with monoclonal antibodies, convalescent serum, or direct-acting antiviral agents
New Text	1. Considered at high-risk of developing severe illness from COVID-19 defined as ≥1 CDC underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (see Appendix 5) AND 2. Unvaccinated against SARS-CoV-2 (defined as having not completed a primary vaccination series) AND 3. Any SARS-CoV-2 vaccination within 3 months prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period AND 5. Currently begin treated or expected to be treated for COVID-19 with monoclonal antibodies, convalescent serum, or direct-acting antiviral agents (all potential subjects should be informed of evolving treatment options during informed consent that alternate therapies may or may not be available to them outside of study participation)
Rationale for Change	Formatted numbering. Excluded unvaccinated subjects from study participation at request of Advarra IRB. Clarified exclusion of subjects who have at least one CDC defined risk factor for developing severe COVID-19 illness (listed in Appendix 5) and by denoting that if subjects have begun treatment or expect to begin treatment of listed products, then they meet definition of high-risk and must be excluded. All subjects (qualified or not) should be informed of available COVID-19 treatment options to reduce risk of severe COVID-19 disease progression.

Section and page	5.1.1. Randomization, Page 35
Original Text	Randomization will be stratified as follows: • SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization • Vaccinated (ie, ≥1 dose of an approved vaccine) versus unvaccinated • PK substudy participation versus nonparticipation
New Text	Randomization will be stratified as follows: • SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization

	• Received primary vaccination series, alone versus any booster shots • PK substudy participation versus nonparticipation
Rationale for Change	Unvaccinated subjects excluded from participation at request of Advarra IRB. Stratification will now include subjects who have received primary vaccination only versus subjects who have a least one COVID-19 booster.

Section and page	6.3.1. Screening Visit, Page 39-40
Original Text	• Testing for SARS-CoV-2 N-antibodies using the Roche Elecsys ® Anti-SARS-CoV-2 assay • AND • Blood sample collection for the following analyses: hematology, chemistry, serology (HIV-1, HBV, HCV, SARS-CoV-2), serum pregnancy test (women of childbearing potential only, see Appendix 3)
New Text	*Text Deleted* AND • Blood sample collection for the following analyses: serum pregnancy test (women of childbearing potential only, see Appendix 3)
Rationale for Change	Blood draws for serology tests: SARS-CoV-2 N-antibodies using the Roche Elecsys ® Anti-SARS-CoV-2 assay, HIV-1, HBV, and HCV will only be done as part of baseline assessments to limit blood draw from patient.

Section and page	6.3.2. Baseline/Day 1 Assessments, Page 40-41
Original Text	*New Text Inserted* • Blood sample collection for the following analyses: hematology, chemistry, serology (HIV-1, HBV, HCV, SARS-CoV-2), serum pregnancy test (women of childbearing potential only, see **Appendix 3**) *New Text Inserted*
New Text	• Testing for SARS-CoV-2 N-antibodies using the Roche Elecsys® Anti-SARS-CoV-2 assay • Blood sample collection for the following analyses: hematology, chemistry, serology (HIV-1, HBV, HCV), coagulation panel, serum pregnancy test (women of childbearing potential only, see **Appendix 3Error! Reference source not found.**) • Urine sample collection for urinalysis

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Rationale for Change	Correcting that all serology tests are completed as part of Baseline/Day 1 assessments, only. Corrected body text to match Table 1, Study Procedures Table.

Section and page	6.5. Posttreatment Assessments, Page 42
Original Text	Subjects who experience a relapse in symptom(s) after having no COVID-19 symptom(s) for ≥3 days or have a positive RAT (or clinic qRT-PCR test) after testing negative by RAT or qRT-PCR will be requested to return to clinic within 2 days for MT swab and saliva samples for RAT, IVA, qRT-PCR, and sequencing.
New Text	Subjects who experience a relapse in symptom(s) after having no COVID-19 symptom(s) for ≥3 days or have a positive RAT (or clinic qRT-PCR test) after testing negative by RAT or qRT-PCR will be requested to return to clinic within 2 days for symptom-drive physical examination, vital signs, MT swab and saliva samples for RAT, IVA, qRT-PCR, and sequencing, household transmission survey, and review of AEs and concomitant medications
Rationale for Change	Added vital signs, AE and concomitant medicatin review to ad hoc rebound visits to ensure pulse oximetry is collected as part of safety monitoring for potential severe COVID-19 disease progression and optional household transmission survey for future analysis of rebound or reinfection.

Section and page	Section 6.7. Pharmacokinetic Assessments, Page 42-43
Original Text	Plasma samples will be collected for measurement of PBI-0451 concentrations and estimation of PK parameters (and metabolite**[s]**, as applicable). Plasma collection for subjects participating in the intensive PK substudy may occur at any study visit from Day 1 (the first dose of study drug) to Day 5. Samples will be drawn at the following time points relative to PBI-0451 dosing:
New Text	Plasma samples will be collected for measurement of PBI-0451 concentrations and estimation of PK parameters (and metabolite**[s]**, as applicable). Some subjects will have PK assessed by sparse sampling and other subjects by intensive PK substudy. Plasma collection for subjects participating in the intensive PK substudy may occur at any study visit from Day 1 (the first dose of study drug) to Day 5. Samples for the intensive PK substudy will be drawn at the following time points relative to PBI-0451 dosing:
Rationale for Change	Clarification of text for comprehension of sparse PK sampling and intensive PK substudy sampling.

Section and page	Section 6.8. Safety Assessments, Page 43
Original Text	Safety will be evaluated throughout the study. Refer to **Table 1** for the schedule of assessments. Collection of any additional assessments for routine safety monitoring at additional time points is at the discretion of the investigator based on GCP

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New Text	Safety will be evaluated throughout the study, including physical examinations, vital signs, 12-lead ECG, laboratory studies (hematology, coagulation panel, chemistry, urinalysis), and review of AEs. Refer to **Table 1** for the schedule of assessments. Collection of any additional assessments for routine safety monitoring at additional time points is at the discretion of the investigator based on GCP
Rationale for Change	Body text expanded to reflect specific Safety Assessment in Table 1 for clarity.

Section and page	6.8.2. Patient Reported Outcomes, Page 43
Original Text	• COVID-19 symptoms questionnaire • Hospitalizations or acute/critical care visits (eg, nonadmitted hospital or other care facility) that have occurred since the last study visit
New Text	• COVID-19 symptoms questionnaire • COVID-19 weekly questionnaire • Hospitalizations or acute/critical care visits (eg, nonadmitted hospital or other care facility) that have occurred since the last study visit
Rationale for Change	Weekly COVID-19 questionnaire added at request of FDA.

Section and page	6.8.3. Household Transmission Survey, Page 44
Original Text	Subjects may complete the optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members as outlined in **Table 1.**
New Text	Subjects may complete the optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members as outlined in **Table 1.** No specific identifying information will be collected.
Rationale for Change	Clarifying no specific identifying information will be collected as part of household transmission survey to protect individual identities.

Section and page	6.8.6 Vital Signs, Page 44
Original Text	The schedule of vital signs assessments is provided in **Table 1.** Vital sign measurements include blood pressure, heart rate, respiration rate, and temperature and should be taken once subjects have been seated or in the supine position for a minimum of 5 minutes. A subject's position for measurement should remain consistent throughout the study

New Text	The schedule of vital signs assessments is provided in **Table 1.** Vital sign measurements include blood pressure, heart rate, respiration rate, pulse oximetry, and temperature and should be taken once subjects have been seated or in the supine position for a minimum of 5 minutes. A subject's position for measurement should remain consistent throughout the study.
Rationale for Change	Updated text to include pulse oximetry as part of vital signs assessments.

Section and page	6.8.8.1 Blood Samples, Page 45
Original Text	• Serology (SARS-CoV-2 [using the Roche Elecsys® Anti-SARS-CoV-2 assay], HIV-1, HBV [hepatitis B serum antigen; hepatitis B core antibody], HCV [hepatitis C antibody, reflex to HCV RNA])
New Text	• Serology (SARS-CoV-2 N-antibodies [using the Roche Elecsys® Anti-SARS-CoV-2 assay], HIV-1, HBV [hepatitis B serum antigen; hepatitis B core antibody], HCV [hepatitis C antibody, reflex to HCV RNA])
Rationale for Change	Additional detail of SARS-CoV-2 antibody test at request of FDA

Section and page	6.8.9. Creatinine Clearance and Estimated Glomerular Filtration Rate, Page 45
Original Text	Weight will be collected at screening to calculate CL_{CR} and eGFR.
New Text	Weight will be collected at Baseline/Day 1 to calculate CL_{CR} and eGFR.
Rationale for Change	Body weight collected at Baseline/Day 1 for consistency with safety laboratory draws.

Section and page	Section 7.8. Medical Monitoring, page 55-56
Original Text	*New Text Inserted*
New Text	A team of medically qualified individuals, including but not limited to, the Sponsor and the CRO Medical Monitors, and the Drug Safety Consultant are responsible for ongoing review of all AEs, concomitant medications, laboratory values (including virology), and vital signs (including pulse oximetry), worsening of symptoms (COVID-19 symptom questionnaire, including dyspnea), acute/critical care visits (eg, nonadmitted hospital or other care facility), and study drug discontinuations, at a minimum monthly basis throughout the study, per the Safety Monitoring Plan. Serious adverse events (eg, hospitalizations, life threatening events, medically important events, deaths) will be evaluated by the Sponsor and the CRO Medical Monitor within 24 hours after being reported by the Investigator. Blinded study data will be evaluated for trends and any event which occurs in greater frequency will be evaluated for updating risk language and notifying the IRB and regulatory authorities, as required.

	An independent select team that will not participate in any other study-related activities will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing (See Section 5.1.2), which may include, but not limited to, study termination or modification of the study to protect subject safety.
Rationale for Change	Medical Monitoring responsibilities and details added to protocol at request of Advarra IRB to ensure subject safety through study conduct.

Section and page	Section 9.1.1. Good Clinical Practice, page 57
Original Text	*New Text Inserted*
New Text	Investigators should review all available treatment options for each individual potential subject, including those outside of this study, and risks associated with possibly receiving placebo with the potential subject. The Investigator should refer to the "NIH Treatment Guidelines" (NIH 2022), and the CDC "Interim Clinical Considerations for COVID-19 Treatment in Outpatients" and "Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals" to appropriately discuss the alternative options and risks for being in this study (CDC 2022). The potential subject should also be referred or receive a printout of the CDC "People with Certain Medical Conditions" and "COVID-19 Treatments and Medications" which includes language appropriate for the lay person regarding medical conditions attributed to a higher risk of severe COVID-19 and potential treatment (CDC 2022).
Rationale for Change	Add text to emphasize importance of Investigators utilizing consistent CDC and NIH guidance to inform patients on evolving guidelines and access to treatment availability outside of this clinical trial or as part of rescue therapy.

Investigator Acknowledgement:	

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19
Sponsor:	Pardes Biosciences, Inc. 2173 Salk Avenue PMB #052 Carlsbad, CA 92008
IND Number:	158228
EudraCT Number:	2022-001195-33
ClinicalTrials.gov Identifier:	Not available
Indication:	Treatment and prevention of SARS-CoV-2 infection and associated diseases (ie, COVID-19)
Protocol ID:	PBI-0451-0002
Contact Information:	The medical monitor's name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original 07 July 2022 Amendment 1 26 August 2022

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Pardes Biosciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable institutional review board or independent ethics committee. The information is to be used only by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Pardes Biosciences, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration (2021)
CL_{CR}	creatinine clearance
CoV	coronavirus
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CVAP	Clinical Virology Analysis Plan
CYP	cytochrome P450
DAA	direct-acting antiviral
DDI	drug-drug interaction
EC_{50}	concentration (or dose) effective in producing 50% of the maximal response
EC_{90}	concentration (or dose) effective in producing 90% of the maximal response
ECG	electrocardiogram
(e)CRF	(electronic) case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ET	early termination (visit)
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GPCR	G protein-coupled receptor
HBV	hepatitis B virus
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HCoV	human coronavirus
HCV	hepatitis C virus
HIV(-1)	human immunodeficiency virus (Type 1)
IB	Investigator's Brochure
ICF	informed consent form

ICH	International Conference for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
IVA	infectious virus assay
IXRS	interactive voice and web response system
LOD	limit of detection
mAb	monoclonal antibody
MERS	Middle East respiratory syndrome
(m)ITT	(modified) intention-to-treat
M^{pro}	main protease
MT	mid-turbinate
NAAT	nucleic acid amplification test
PK	pharmacokinetic(s)
P-gp	P-glycoprotein
PTM	placebo-to-match
PVE	pharmacovigilance
(q)RT-PCR	(quantitative) reverse transcriptase polymerase chain reaction
RAT	rapid antigen test
RNA	ribonucleic acid
RTV	ritonavir
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOP	standard operating procedure
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
$TCID_{50}$	median tissue culture infectious dose

PROTOCOL SYNOPSIS

Pardes Biosciences, Inc.
2173 Salk Ave. Suite 250
PMB #052
Carlsbad, CA 92008

Study Title: A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19

IND Number: IND 158228

EudraCT Number: 2022-001195-33

Study Centers Planned: Up to 100 study centers are planned.

Objectives and Endpoints:

Primary Objective	Primary Endpoint
• To evaluate the antiviral activity of PBI-0451	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA) from mid-turbinate (MT) swabs
Secondary Objectives	**Secondary Endpoint**
• To evaluate safety and tolerability of PBI-0451	• Number of treatment-emergent adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, and Grade 3 or 4 laboratory abnormalities
• To evaluate clinical efficacy of PBI-0451 versus placebo through study Day 28	• Proportion of subjects with sustained symptom resolution through Day 28 • Time to sustained symptom resolution through Day 28 • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 • Severity of targeted COVID-19 symptoms

	• Number of COVID-19 related medical visits other than hospitalization, including acute/critical care visits through Day 28 • Number of days in any hospital unit for treatment of COVID-19
• To evaluate the effect of PBI-0451 on SARS-CoV-2	• Presence of SARS-CoV-2 virus, viral RNA or viral antigen based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate SARS-CoV-2 resistance to PBI-0451	• Sequence analysis of the SARS-CoV-2 main protease (M^{pro}) gene (nsp5) and M^{pro} cleavage sites
• To evaluate SARS-CoV-2 resistant variant susceptibility to PBI-0451	• Susceptibility analysis of SARS-CoV-2 variants with M^{pro} amino acid substitutions and variants with substitutions in M^{pro} cleavage sites in the SARS-CoV-2 polyprotein
• To evaluate the relationship between SARS-CoV-2 detection methods	• Correlation of SARS-CoV-2 detection by IVA, RAT, and qRT-PCR, as specified in the CVAP
• To evaluate the incidence of rebound SARS-CoV-2 infection	• Proportion of subjects with clinical and/or virologic rebound
• To evaluate PBI-0451 pharmacokinetics (PK)	• PBI-0451 PK analysis from an intensive PK substudy of up to 50 subjects • PK parameters from sparse sampling of all subjects for population PK analysis
Study Design: Phase 2, double-blind, randomized, placebo-controlled study	
Number of Subjects Planned: Approximately 210 subjects will be randomized.	

Target Population: Nonhospitalized, symptomatic male and nonpregnant, nonlactating female subjects 18 to < 65 years of age with a positive direct test of SARS-CoV-2 infection (antigen based or nucleic acid amplification test [NAAT]) who are not at high-risk of progressing to severe disease

Duration of Treatment: 5 days

Study Duration: Up to 28 days of assessments (ie, the study period) and a Week 24 follow-up to assess symptoms and survival status

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria

1. Can understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of any study procedures.
2. Onset of COVID-19 symptoms ≤ 5 days prior to randomization with a positive SARS-CoV-2 test ≤ 24 hours prior to randomization. Authorized NAAT or antigen tests that detect viral RNA or protein, respectively, are allowed.
3. Received primary vaccination series as defined by Centers for Disease Control and Prevention (CDC). Subjects should be advised during informed consent that alternate therapies may be available outside of study participation.
4. ≥ 2 symptoms of acute COVID-19 infection as determined by the investigator from the symptoms listed on the COVID-19 symptoms questionnaire present at randomization
5. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or in a postmenopausal state (see Appendix 3).
6. Male and female subjects and/or their heterosexual partners must either be of nonchildbearing potential or must use effective contraception from screening through 90 days after the last dose of study drug (see Appendix 3)
7. Female subjects must refrain from egg donation and in vitro fertilization during treatment and for ≥ 28 days after the last dose of study drug
8. Male subjects must refrain from sperm donation from screening through 90 days after the last dose of study drug
9. Normal 12-lead electrocardiogram (ECG) evaluation without clinically significant abnormalities
10. Able and willing to comply with all study requirements

Exclusion Criteria

1. Considered at high-risk of developing severe illness from COVID-19 defined as ≥ 1 CDC underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (see Appendix 5)
2. Unvaccinated against SARS-CoV-2 (defined as having not completed a primary vaccination series)
3. Any SARS-CoV-2 vaccination within 3 month prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period
4. Currently hospitalized or expected to require hospitalization for COVID-19 within 48 hours of randomization
5. Currently being treated or expected to be treated for COVID-19 with monoclonal antibodies, convalescent serum, or direct-acting antiviral agents (all potential subjects should be informed of evolving treatment options during informed consent that alternate therapies may or may not be available to them outside of study participation)
6. Any clinical condition or laboratory result considered by the investigator to indicate any unstable or poorly controlled underlying clinically significant medical condition(s), active disseminated infection (other than SARS-CoV-2), or other medical condition that could represent a risk to the subject, including increasing the likelihood of a safety event, affect subject compliance, or affect efficacy and/or safety data collected during the 28-day study period
7. Known active liver disease, including nonalcoholic steatohepatitis/nonalcoholic fatty liver disease, chronic or active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, primary biliary cirrhosis, Child-Pugh Class B or C, chronic alcoholic liver disease, or acute liver failure
8. Receiving dialysis or having known severe renal impairment (chronic kidney disease, Stage 4 or above)
9. Unable or unwilling to comply with the protocol procedures
10. Participating in another interventional study with an investigational compound or device, including those for COVID-19
11. Known prior participation in this study or another study involving PBI-0451
12. Females who are pregnant or breastfeeding
13. Oxygen saturation of < 94% on room air

Study Procedures/Frequency: Following completion of screening and eligibility assessments, eligible subjects will be randomized 2:1 to one of 2 treatment groups on Day 1 as follows:

- PBI-0451: 2 × 350 mg tablets administered orally twice daily (BID) (1400 mg/day) with food for 5 days (10 total doses)
- Placebo: 2 × placebo to match PBI-0451 tablets administered orally BID with food for 5 days (10 total doses)

Randomization will be stratified as follows:

- SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization
- Received primary vaccination series, alone versus any booster shots
- PK substudy participation versus nonparticipation

Note: Screening assessments may be considered as baseline/Day 1 assessments if the subject meets eligibility requirements, is randomized, and receives the first dose of study drug on same day.

Study Visits: Following randomization on Day 1, subjects will complete baseline assessments prior to receiving their first dose of study drug (PBI-0451 or placebo). All subjects will have additional safety and efficacy assessments during the 28-day study period.

A follow-up visit (eg, telephone visit, virtual visit, clinic visit, etc**.** as convenient) will be conducted at Week 24 (± 20 days) after the last dose of study drug for all subjects. Information regarding ongoing or recurrent COVID-19 symptoms, survival status, pregnancy status (for female subjects of childbearing potential and female partners of male subjects), and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) that have occurred since the last study visit will be collected.

Study Drug Administration: Subjects will take their first dose of study drug (PBI-0451 or placebo) with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1 to ensure that a full total daily dose (1400 mg PBI-0451) is taken on the first day of treatment. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of the 5 days of treatment.

Patient-Reported Outcomes: Subject self-reports will be assessed daily at screening, Days 1 through 28 or early termination (ET), and the Week 24 follow-up as follows:

- COVID-19 symptom questionnaire
- COVID-19 weekly questionnaire
- COVD-19 related hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) since the last study visit

Hospitalization is defined as > 24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19. This includes any special medical care unit within an assisted living facility or nursing home.

- Optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members (baseline/Day 1 and Days 5, 10, 15, 28 or ET only, and rebound ad hoc visit (if applicable))

Serology Testing: Serology samples at screening and/or baseline/Day 1:

- SARS-CoV-2 N-antibodies (using the Roche Elecsys® Anti-SARS-CoV-2 assay)
- Human immunodeficiency virus Type 1
- HBV (hepatitis B serum antigen; hepatitis B core antibody)
- HCV (hepatitis C antibody, reflex to HCV RNA)

Virologic Assessments: The following tests will be performed from mid-turbinate (MT) nasal swab and saliva samples at screening, baseline/Day 1, and Days 2, 3, 5, 10, 15, 28 or early termination (ET), and rebound ad hoc visit (if applicable)

- SARS-CoV-2 qRT-PCR (MT swab and saliva)
- SARS-CoV-2 RAT (MT swab)
- SARS-CoV-2 IVA (MT swab and saliva) at baseline/Day 1 and Days 2, 3, 5, 10, Day 15, rebound and early termination
- SARS-CoV-2 sequence analysis (MT swab) at baseline/Day 1 and Day 5 for all subjects to evaluate the potential for the development of resistance in response to treatment with PBI-0451. Additional time points may be evaluated in the case of virologic rebound or if the subject remains viremic at other study visits (ie, if SARS-CoV-2 RNA by qRT-PCR is ≥ 3.85 $\log_{10}$ copies/mL, which is the threshold for the minimum amount of viral RNA required for whole genome sequencing).

RAT will be conducted for subjects at the study clinic with results recorded in real time. All other MT and saliva samples will be shipped to the central laboratory on the day of collection for subsequent qRT-PCR and IVA testing.

Note: SARS-CoV-2 RAT or qRT-PCR tests for household members will not be performed at the study clinic; that data will be captured as part of an optional self-reported assessment of confirmed SARS-CoV-2 infections in household members.

Safety Assessments:

- Complete physical examination: Screening and baseline/Day 1 and Day 28 or ET
- Symptom-driven physical examination: Days 2, 3, 5, 10, and 15
- Vital signs: All visits through Day 28
- 12-lead ECG: Screening; baseline/Day 1 (predose;) and Days 5, 10, and 28 or ET
- Clinical laboratory blood draws (hematology and chemistry) and urinalysis: baseline/Day 1 (predose) and Days 5, 10, and 28 or ET
- Serum/urine pregnancy test (females of childbearing potential only): Screening, baseline/Day 1, and Day 28 or ET

Medical Monitoring

A team of medically qualified individuals, including but not limited to, the Sponsor and the CRO Medical Monitors, and the Drug Safety Consultant are responsible for ongoing review of all AEs, concomitant medications, laboratory values (including virology), and vital signs (including pulse oximetry), worsening of symptoms (COVID-19 symptom questionnaire, including dyspnea), acute/critical care visits (eg, nonadmitted hospital or other care facility), and study drug discontinuations, at a minimum monthly basis throughout the study, per the Safety Monitoring Plan. Serious adverse events (eg, hospitalizations, life threatening events, medically important events, deaths) will be evaluated by the Sponsor and the CRO Medical Monitor within 24 hours after being reported by the Investigator. Blinded study data will be evaluated for trends and any event which occurs in greater frequency will be evaluated for updating risk language and notifying the IRB and regulatory authorities, as required.

Rescue Therapy

Subjects who experience severe COVID-19 illness (defined in this study as sustained pulse oximetry <94%, a respiratory rate of >30 breaths/min, or dyspnea that requires medical attention) should discontinue study drug and be immediately referred by the Investigator to emergency care or treated by the Investigator for standard of care treatment of symptoms including, but not limited to, other antivirals, supplemental oxygen, corticosteroids, Janus kinase inhibitors, or interleukin-6 blockers, in accordance with the NIH Treatment Guidelines (NIH 2022). The subject should continue participation in the study, with study drug discontinued, for safety follow-up and clinical outcome of the medically attended visit.

Pharmacokinetic Assessments:

- All subjects will have single PK blood draws at baseline/Day 1 (after first dose of study drug) and Day 5, with the time of the blood draw relative to the last dose of study drug recorded.
- An intensive PK substudy will be conducted in a subset of up to 50 subjects at select sites who provide separate specific consent. Intensive PK blood draws will be collected at the following time points: predose (ie, ≤ 5 minutes of dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and (optional) 10 to 12 hours postdose. Intensive PK sampling may occur on any treatment day (ie, baseline/Day 1 [after first dose of study drug] through Day 5).

Any remaining PK samples will be stored and may be used for exploratory assessments, such as metabolites, protein binding, endogenous markers of drug-drug interactions, biomarkers of host responsiveness, and other investigational experiments.

Test Product, Dose, and Mode of Administration: 2 × 350 mg tablets administered orally BID (1400 mg/day) with food for 5 days (10 total doses)

Subjects will take their first dose with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1 to

ensure that a full total daily dose (1400 mg PBI-0451) is taken on the first day of treatment. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of 5 days of treatment
Reference Therapy, Dose, and Mode of Administration: 2 × placebo to match PBI-0451 tablets administered orally BID for 5 days (10 total doses). Subjects will take their first dose with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of 5 days of treatment
Statistical Methods: Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan. Summary statistics will be used to analyze the study data. Any statistical testing will be conducted to ensure that the overall alpha = 0.05 level (2 sided). Unless otherwise specified, the data summaries and analyses described below will be reported by treatment group. The modified intention-to-treat (mITT) analysis set includes all randomized subjects with ≥ 2 symptoms consistent with COVID-19 ≤ 5 days prior to randomization and a positive SARS-CoV-2 test (RT-PCR or RAT) ≤ 24 hours prior to randomization who received ≥ 1 dose of study drug. This is the primary analysis set for all clinical endpoints. The mITT virologic analysis set is a subset of the mITT analysis set that includes subjects who had detectable infectious SARS-CoV-2 by IVA at baseline/Day 1. This is the primary analysis set for the primary efficacy endpoint. **Efficacy:** The primary efficacy endpoint is the proportion of subjects below the LOD for infectious SARS-CoV-2 on Day 3 by IVA. For the primary endpoint, differences between PBI-0451 and placebo will be evaluated using stratum-adjusted Mantel-Haenszel proportions (adjusted for randomization strata). The proportion of subjects below the LOD for infectious SARS-CoV-2 at other time points will be summarized in a similar manner. The time to resolution of targeted COVID-19 symptoms will be estimated with the Kaplan-Meier method and summarized by treatment group. Differences between treatment groups will be determined using a Wilcoxon-Gehan test. The analysis of time to resolution of each targeted COVID-19 symptom will be conducted in a similar manner. The proportion of subjects with COVID-19 related hospitalization or death from any cause will be summarized by treatment group. Differences between treatment groups will be assessed using Mantel-Haenszel proportions. The number of COVID-19 related hospitalizations or acute/critical care visits and the number of days in any hospital unit for the treatment of COVID-19 will be summarized. Differences between treatment groups will be assessed using a van Elteren test stratified by the randomization factors.

SARS-CoV-2 viral load kinetics will be summarized by study visit. Differences between the treatment groups will be assessed with a van Elteren test stratified by the randomization factors.

SARS-CoV-2 clinical and virologic rebound will be summarized by the amount of viral RNA detected at baseline/Day 1, time to loss of clinical symptoms, time to negative RAT or IVA, and time to the first confirmed reappearance of symptoms and/or a positive RAT or qRT-PCR sample.

A correlation of the results of IVA, RAT, and qRT-PCR assessments will be evaluated.

Virologic outcomes will be summarized by subject serology status determined using the Roche Elecsys Anti-SARS-CoV-2 assay, which uses a recombinant protein representing the nucleocapsid (N) antigen to detect antibodies against SARS-CoV-2.

Safety: The safety analysis set includes all randomized subjects who received ≥ 1 dose of study drug. This is the primary analysis set for safety analyses.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. Treatment-emergent AEs, SAEs, and AEs leading to premature discontinuation of study drug/study will be summarized by treatment, system organ class, and preferred term.

Laboratory results and change from predose values for selected laboratory tests will be summarized by treatment at scheduled visits. The incidence of treatment-emergent laboratory abnormalities (Division of AIDS Toxicity Grading Scale) will be summarized by treatment.

Pharmacokinetics: The PK analysis set includes all subjects who participated in the intensive PK substudy and have ≥ 1 nonmissing PK concentration reported by the PK laboratory. This is the primary analysis set for PK analyses.

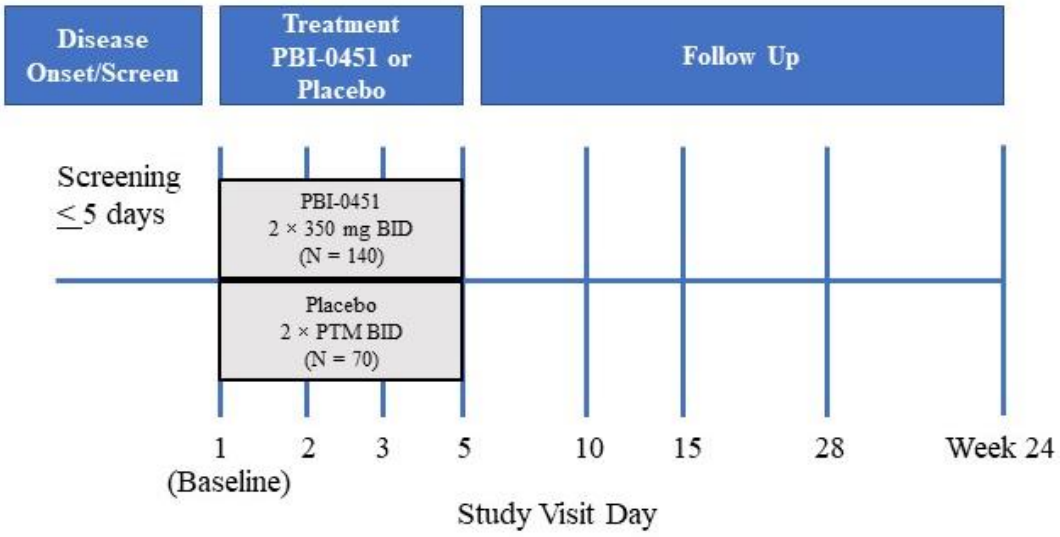
PBI-0451 plasma concentrations and PK parameters will be derived using noncompartmental methods (including metabolite[s] as applicable) and listed and summarized using descriptive statistics.

PBI-0451 plasma concentrations from the PK substudy and sparse sampling from the overall study population will be used in a population PK analysis and reported separately.

Sample Size: The sample size will be approximately 210 subjects to account for approximately 60% of randomized subjects who are anticipated to be SARS-CoV-2 negative by IVA at baseline/Day 1 and would be excluded from the mITT virologic analysis set. It should be noted that this sample size is sufficient with ≥ 80 power to detect a > 19% absolute difference in the proportion of subjects below the LOD for infectious SARS-CoV-2 virus (99% vs 81%) at Day 3 by IVA among subjects who had detectable infectious SARS-CoV-2 at baseline/Day 1. This assumes alpha = 0.05 and that 40% of subjects have detectable infectious virus at baseline/Day 1.

STUDY SCHEMA

Figure 1. Study PBI-0451-0002: Study Schema



BID = twice daily; PTM = placebo to match

STUDY PROCEDURES TABLE

Table 1. Study PBI-0451-0002: Study Procedures Table

	Screening[a] (Day -5 to Day 1)	Baseline/Day 1[b]	Day 2	Day 3	Day 5 (±1 day)	Day 10 (±2 days)	Day 15 (±2 days)	Rebound Ad Hoc Visit[d]	Day 28 (±3 days)	Week 24 Follow Up (±20 days)[e]	ET
Written Informed Consent	X										
Medical History	X										
Complete Physical Examination	X	(X)							X		X
Symptom-Driven Physical Examination			X	X	X	X	X	X			
Height	X										
Weight	X	(X)							X		X
Vital Signs[f]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 N-antibodies		X									
SARS-CoV-2 RAT[g]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 qRT-PCR Test[g]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 Sequence Analysis[g,h]	X	(X)	(X)	(X)	X	(X)	(X)	X	(X)		(X)
SARS-CoV-2 IVA[g]	X	(X)	X	X	X	X	X	X			(X)
HIV-1, HBV (HbsAg and HbcAb), and HCV (HCV antibody reflex to HCV RNA) Testing		X									
12-Lead ECG	X	(X)			X	X			X		X
Optional Genomic Sample		X									
Hematology[i]		X			X	X			X		X

	Screening[a] (Day -5 to Day 1)	Baseline/Day 1[b]	Day 2	Day 3	Day 5 (±1 day)	Day 10 (±2 days)	Day 15 (±2 days)	Rebound Ad Hoc Visit[d]	Day 28 (±3 days)	Week 24 Follow Up (±20 days)[e]	ET
Coagulation Panel		X			X	X			X		X
Chemistry[j]		X			X	X			X		X
Urinalysis[k]		X			X	X			X		X
Creatinine Clearance and eGFR		X			X	X			X		X
Serum/Urine Pregnancy Test[l]	X	(X)							X		X
Study Drug Dispensing		X									
Study Drug Administration		2 × 350 mg PBI-0451 or Placebo BID orally for 5 days (10 total doses)									
Patient Reported Outcomes[m]	X	(X)	X							X	X
Intensive PK Sampling[n]		X									
Single PK Sample[o]		X			X						
Household Transmission Survey[p]		X			X	X	X	X	X		X
Survival Status[q]					X	X	X		X	X	
Review and Assess AEs and Concomitant Medication[r]	X	(X)	X	X	X	X	X	X	X		X

AE = adverse event; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HbcAb = hepatitis B core antibody; HbsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV-1 = human immunodeficiency virus Type 1; IVA = infectious virus assay; PK = pharmacokinetics; qRT-PCR = quantitative reverse-transcriptase polymerase chain reaction; RAT = rapid antigen test; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

a. Prospective subjects should be screened ≤ 5 days prior to administration of first dose of study drug (ie, randomization/Day 1)
b. Screening assessments may be considered as baseline/Day 1 if the subject is eligible for the study and is randomized and receives the first dose of study drug on that day. Parentheses indicate that assessment is not required if performed at screening, and screening and baseline/Day 1 are the same.
c. Individual study visits must occur on separate calendar days within the visit window, with the time(s) of sample collection recorded.

d. Subjects who experience a relapse in symptom(s) after having no COVID-19 symptom(s) for ≥3 days or have a positive RAT (or clinic qRT-PCR test) after testing negative by RAT or qRT-PCR will be requested to return to clinic within 2 days for mid-turbinate nasal swab and saliva samples for RAT, qRT-PCR, and sequencing.
e. Week 24 visit performed via telephone visit, virtual visit, or clinic visit, as convenient.
f. Vital signs include blood pressure, heart rate, respiratory rate, pulse oximetry and temperature (predose and postdose on Day 1).
g. Mid-turbinate nasal swabs will be collected to measure SARS-CoV-2 using qRT-PCR, IVA, RAT, and viral sequencing. Saliva samples will be collected to measure SARS-CoV-2 using qRT-PCR and IVA. Parentheses indicate sample at ET visit if the subject discontinues treatment prior to Day 10.
h. SARS-CoV-2 sequence analysis (nasal mid-turbinate sample) will be conducted only if the subject is viremic and above the limit of detection (LOD) of the sequencing assay. Sequence analysis may be conducted on samples obtained at other study visits for subjects who experience virologic rebound or if the subject remains viremic through Day 28. Parentheses indicate sequencing samples where sequencing is dependent on the subject being viremic and experiencing virologic rebound and viral RNA is above the LOD of the sequencing assay by qRT-PCR.
i. Hematology includes complete blood count with differential and platelets.
j. Serum chemistry includes comprehensive metabolic panel.
k. Urinalysis includes microscopic reflex.
l. Pregnancy tests for females of childbearing potential only; screening urine test required for eligibility.
m. Self-reported daily assessment of targeted COVID-19 symptoms (per the COVID-19 symptoms questionnaire) and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) will be assessed daily and weekly at screening and from baseline/Day 1 through Day 28.
n. Intensive PK sampling for substudy subjects only. Sampling will occur relative to study drug administration at the following times: predose (ie, ≤ 5 minutes prior to dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and (optional) 10-12 hours postdose; intensive PK sampling will occur on any day of treatment from Day 1 (subject's first dose of study drug) to Day 5.
o. Sparse PK samples will be obtained at baseline/Day 1 (subsequent to subject's first dose of study drug) and Day 5.
p. Optional subject self-reported assessment of number of confirmed SARS-Co V-2 infections (RAT or qRT-PCR) in household members. No specific identifying information will be collected.
q. Survival status also includes current supplemental oxygen use, pregnancy status (for female subjects of childbearing potential and female partners of male subjects), and any hospitalizations or acute/critical care visits that occurred since the last study visit during the 28-day study period.
r. All AEs recorded from the time of obtaining informed consent through Day 28; all ongoing AE's will be followed to resolution or condition is considered permanent.

1. INTRODUCTION

1.1. Background

Pardes Biosciences, Inc. (hereafter referred to as Pardes) is developing PBI-0451, a new chemical entity and orally bioavailable direct-acting antiviral (DAA) inhibitor of the main protease (M^{pro}) of coronaviruses (CoVs), including the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes Coronavirus Disease 2019 (COVID-19) (Jin et al. 2020). PBI-0451 is an investigational agent that, by inhibiting the ability of the virus to replicate, has the potential for use as treatment and prevention of SARS-CoV-2 infection and associated diseases (ie, COVID-19). Additionally, it is anticipated that an effective DAA may reduce the magnitude and duration of viral shedding of replicating virus and therefore reduce the likelihood of transmission of SARS-CoV-2.

CoVs are positive, single-stranded RNA viruses, of which 7 infect humans and are believed to result in 5% to 30% of "common colds" for which therapeutic intervention is generally limited to over-the-counter symptomatic relief (Paules et al. 2020). CoV infection in humans is transmitted from person to person via shedding of replicating virus within the respiratory tract through aerosolization (Tang et al. 2020) (Tang et al. 2020). SARS-CoV-2 is a novel strain of CoV discovered in late 2019 and responsible for COVID-19 that can range from mild to severe disease with symptoms, including extreme fatigue and dyspnea, that can be short-lived or prolonged (eg, "long COVID") with some cases developing pneumonia that can progress into acute respiratory distress syndrome and sometimes death, despite aggressive supportive care(Tang, Comish, and Kang 2020) (Tang et al. 2020) (Sharma et al. 2020) (Marshall 2020) (Marshall 2020). All persons are at risk for infection with SARS-CoV-2 and developing COVID-19. SARS-CoV-2 represents the third novel CoV (in addition to SARS-Co-V and Middle East respiratory syndrome [MERS] CoV) to make a zoonotic transfer in the last 2 decades and result in significant human disease (Dhama et al. 2020). The potential for new CoV outbreaks is likely to continue.

Natural history data for nonpandemic CoV infection has established that reinfection with the same or different strains of CoV (including SARS-CoV-2) can occur (Tillett et al. 2021) (Harvey et al. 2021). Moreover, throughout the pandemic, surveillance has identified multiple spike protein mutations resulting in the global emergence of several SARS-CoV-2 variants of concern (ie, Delta, Omicron) due to potentially higher levels of transmissibility or immune escape (Korber et al. 2020) (Campbell et al. 2021) (Zella et al. 2021). This is particularly important as CoVs are known to mutate and undergo genetic recombination, which may facilitate transmission, replicative fitness, and pathogenicity across species (Lau and Chan 2015). A consequence of this has already been seen with some monoclonal antibodies (mAbs), where reduced efficacy against emerging SARS-CoV-2 variants (ie, Delta, Omicron) has led to recommendation against their use.

Near-universal vaccination is desired to reduce transmission and severity of COVID-19 disease; however, access to and acceptance of vaccines are suboptimal, and it is unknown if vaccines will

provide adequate duration of protection against current and future SARS-CoV-2 variants (Edridge et al. 2020).

While the details of the pathobiology and risk factors for developing severe COVID-19 disease remain unclear, it is established that early intervention to inhibit viral replication provides clinical benefit. Experience with influenza and emerging evidence with COVID-19 indicates that early treatment via a short course (eg, 5 days) of oral DAA therapy results in less severe disease and that preventing transmission is also possible (Muthuri et al. 2014) (Uyeki et al. 2019) (Chow et al. 2019) (Ikematsu et al. 2020).

Orally administered small molecule protease inhibitors are a clinically validated treatment and a standard of care for multiple viral diseases, including hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections (Ghany and Morgan 2020) (Department of Health and Human Services 2022). These agents can exhibit favorable drug-like properties and a favorable benefit:risk profile, including when used at high doses and exposures in both the short-term (weeks to months in HCV) and chronic (life-long therapy for HIV) settings (Patick and Potts 1998).

Small molecule DAAs that are orally administered and suitable for outpatient use are needed to treat people who become infected and are at high risk for severe COVID-19. In addition, treatment with oral DAAs is warranted to reduce the time to symptom resolution and decrease the duration of shedding infectious virus. Moreover, such agents can also be deployed in "ring prophylaxis" to contacts of infected individuals or in the setting of mitigating the spread of new, localized outbreaks. Small molecule oral DAAs are attractive therapeutics as they target viral and not host processes that may reduce the risk for off-target effects, and thus increase the likelihood of a favorable therapeutic index. Consequently, there remains a high unmet medical need for an easy to use, oral antiviral drug for the treatment and prevention of SARS-CoV-2 infection and associated diseases (ie, COVID-19).

1.2. PBI-0451

1.2.1. General Information

PBI-0451 is an investigational agent that has the potential for use as treatment and prevention of SARS-CoV-2 infection and associated diseases (ie, COVID-19) by inhibiting the ability of the virus to replicate and thereby reduce the incidence and magnitude of the pathologic immune response responsible for the morbidity and mortality associated with severe disease. PBI-0451 is a potent inhibitor of SARS-CoV-2 M^{pro}, an essential enzyme for viral replication with EC_{50} = 23 nM and EC_{90} = 113.5 nM in SARS-CoV-2 antiviral assays. In nonclinical studies, PBI-0451 has broad-spectrum activity against SARS-CoV-2 clinical variants Alpha, Beta, Delta, Epsilon, Gamma, Mu, and Omicron and human coronaviruses (HcoVs) 229E and OC43 in cell-based antiviral assays. It has broad-spectrum activity in in vitro enzyme assays against the M^{pro} from HcoVs SARS, 229E, HKUI, OC43, NL63, and MERS, suggesting that it interacts with the

most essential elements of the M^{pro} binding pocket. This hypothesis is supported by in vitro resistance studies which suggest that PBI-0451 has a high barrier to resistance. In in vivo pharmacodynamic animal model of infection studies in mice, PBI-0451 showed a trend towards improved lung function at the higher PBI-0451 doses that correlated with a 10-fold decrease in viral load in the lung. Screens for off-target activity on host cysteine proteases and other targets revealed no significant concerns. A ritonavir (RTV)-boosted SARS-CoV-2 protease inhibitor, nirmatrelvir [Pfizer]), targeting the same active enzyme pocket has shown significant benefit for high risk COVID-19 patients in the clinic. PBI-0451, at an appropriate dose and dosing regimen, thus has potential to provide similar clinical benefit for SARS-CoV-2-infected patients with PBI-0451.

PBI-0451 has completed toxicology studies conducted under Good Laboratory Practice guidelines, including 14-day studies in mice and dogs without evidence of adverse findings. For further information on PBI-0451, refer to the current Investigator's Brochure (IB).

1.2.2. Preclinical Pharmacology and Toxicology

PBI-0451 has shown a favorable selectivity profile at anticipated clinical exposures relative to activity against a panel of human (and rat) GPCRs, ion channels, transporters, nuclear receptors, and select enzymes (WuXi Mini Safety Panel).

For further information on PBI-0451, refer to the current IB.

1.2.3. Clinical Studies of PBI-0451

As of 1 July 2022, two clinical studies of PBI-0451 have been initiated and have completed clinical assessment: Study PBI-0451-0001 is a first-in-human, single ascending dose/multiple ascending dose study of PBI-0451 with nested food effect and drug-drug interaction (DDI) screening cohorts, and Study PBI-0451-0004 is a relative bioavailability (food effect) study.

Safety

Preliminary clinical data indicate that PBI-0451 has been well tolerated at single and multiple oral doses (ie, 10 days) up to 2100 mg/day. All reported treatment-emergent adverse events (AEs) have been mild or moderate in severity and none have been considered definitely related to study drug. No serious adverse events (SAEs) or deaths have been reported. No clinically significant treatment-emergent laboratory abnormalities, no treatment-emergent AEs due to laboratory abnormalities, and no clinically significant abnormal findings with respect to vital signs or safety electrocardiogram (ECG) assessments have been reported.

Pharmacokinetics

Preliminary clinical data demonstrate that PBI-0451 has a favorable human pharmacokinetics (PK) profile following single and multiple ascending oral doses up to 2100 mg/day. PBI-0451 demonstrates dose-linear exposures when administered with food, achieves rapid systemic

exposures that exceed the target protein-binding adjusted EC_{90} against SARS-CoV-2, and exhibits a 2-compartment PK profile that supports administration as a stand-alone agent when administered with food. PBI-0451 has been shown to be a weak CYP3A4 inhibitor and a nonsensitive substrate of CYP3A4, P-gp, and BCRP. DDI evaluation in vitro; in vivo; and in silico, using physiological-based PK modeling and simulation, indicated that the DDI potential of PBI-0451 as a victim or perpetrator for other major CYP enzymes and transporters is negligible. Overall, the DDI assessments suggest that PBI-0451 presents no to minimal DDI potential at the proposed clinical dose.

1.2.4. Rationale for PBI-0451-0002

PBI-0451 is a new chemical entity intended as an orally available DAA whose mechanism of action is inhibition of the M^{pro} of CoV, including the SARS-CoV-2 that causes COVID-19. Short-term administration (eg, 5 days) of antivirals with similar (nirmatrelvir [Pfizer]) and different (molnupiravir [Merck]) mechanisms of action have been reported to improve the outcomes (hospitalization or death) in nonhospitalized patients with SARS-CoV-2 infection at high risk for severe COVID-19. The incidence of COVID-19 remains high, mainly in unvaccinated persons, but breakthrough infections have also occurred in persons who have been fully vaccinated. PBI-0451 is an oral DAA with broad activity against CoVs, including SARS-CoV-2, and has the potential to address this unmet medical need.

1.3. Rationale for Dose Selection of PBI-0451

Dose selection for PBI-0451 included consideration of all relevant nonclinical and clinical data and knowledge from the development of DAAs used for the treatment of both acute (eg, influenza and COVID-19) and chronic (ie, HIV, hepatitis B virus (HBV), and HCV viral infections) (Department of Health and Human Services 2022) (Ghany and Morgan 2020) with the goal of providing systemic drug exposures that will maximally reduce viral burden. Specifically, the goal is to achieve and maintain (accounting for protein binding) concentration multiples above the EC_{50} (US Food and Drug Administration 2006) and whenever possible also above the EC_{90} over the duration of the dosing interval.

Nonclinical and clinical data support the Phase 2 evaluation of a total daily dose of PBI-0451 1400 mg as 700 mg (2 × 350 mg tablets) BID administered with food for 5 days. This dose has been shown to achieve desired PK exposures. For additional information on PBI-0451 dose selection refer to the current IB.

Due to the desire to rapidly initiate treatment with maximally suppressive drug concentrations against SARS-CoV-2, a loading dose approach has been selected to provide the highest peak and trough PBI-0451 concentrations at the initiation of treatment (ie, Day 1), followed by the establishment of steady-state conditions for the remainder of the treatment period as described in Section 5.3). The dosing regimen is designed to assure initiation of therapy as soon as possible after randomization and administration of the full 1400 mg total daily dose on Day 1 of treatment to provide maximal antiviral activity at the point of highest viral burden and when the potential

DAA benefit is greatest. The safety of this dosing regimen is supported by single and multiple doses equal to or greater in magnitude (up to 2100 mg) and for longer duration (up to 10 days) than proposed in this Phase 2 study.

The duration of treatment in this study is 5 days, consistent with other acute antiviral treatments, such as oseltamivir for influenza. The 5-day treatment duration is identical to that shown to result in reduced rates of clinically meaningful endpoints in DAA treatment studies of COVID-19 (Jayk Bernal et al. 2022) that include SARS-CoV-2 viral load (Sasaki et al. 2022) and hospitalization due to COVID-19 or death from any cause, including nirmatrelvir (an M^{pro} inhibitor with the same mechanism of action of PBI-0451) coadministered with RTV (Hammond et al. 2022).

1.4. Risk/Benefit Assessment for the Study

The overall benefit/risk balance for this study is considered favorable.

The target patient population under study for this protocol is designed to exclude patients who are at high risk of progression to severe COVID-19 and thus for which there may be no approved or authorized treatments.

During a pandemic, additional potential risks to subjects may include interruptions to the study visit schedule and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for details on the risks and risk mitigation strategy.

1.4.1. Risk/Benefit for PBI-0451

No clinical safety issues specifically related to PBI-0451 have been identified to date.

The expected benefit to subjects being treated with PBI-0451 is a rapid decrease of SARS-CoV-2 viral load within a short treatment period, without the need for coadministration of a second agent for pharmacoenhancement and its potential for DDIs and potentially reduce the duration of symptomatic illness and the risk of progression to more severe disease.

Potential risks include unforeseen safety issues, the lack of efficacy and the risk of progression to more severe COVID-19 disease progression. For the population of subjects with SARS-CoV-2 infection, the expected benefit of eliminating SARS-CoV-2 virus within 5 days of treatment outweighs the risks associated with the possible development of previously unidentified safety issues.

1.4.2. Risk/Benefit for Placebo

Subjects randomized to the placebo group may benefit from frequent medical monitoring during the study as there is a potential risk of severe COVID-19 disease progression.

1.4.3. Potential Alternatives to Placebo

Investigators should review all available treatment options for each individual subject, including those outside of this study, and risks associated with placebo with the potential subject. The Investigator should refer to the "NIH Treatment Guidelines" (NIH 2022), and the CDC "Interim Clinical Considerations for COVID-19 Treatment in Outpatients" and "Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals" to appropriately discuss the alternative options and risks for being in this study (CDC 2022). The potential participant should also be referred to or receive a printout of the CDC "People with Certain Medical Conditions" and "COVID-19 Treatments and Medications" which includes language appropriate for the lay person regarding medical conditions attributed to a higher risk of severe COVID-19 and potential treatment (CDC 2022).

1. The following products are either FDA approved or authorized for emergency use for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and are recommended as first line agents by the NIH Treatment Guidelines:

- Veklury (remdesivir) – FDA approved (Gilead Sciences 2022)

- Paxlovid (nirmatrelvir) boosted with ritonavir – Emergency Use Authorization (US Food and Drug Administration 2022c)

2. The following products have emergency use authorization by the FDA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are high risk for progression to severe COVID-19, including hospitalization or death, **and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate** per the NIH Treatment Guidelines.

- Lagevrio (molnupiravir) – Emergency Use Authorization (US Food and Drug Administration 2022a)

- Bebtelovimab – Emergency Use Authorization (US Food and Drug Administration 2022b)

3. The list of approved or authorized products is subject to change during the course of the study, the complete list of FDA products can be found here: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs and the NIH Treatment Guidelines can be found here; https://www.covid19treatmentguidelines.nih.gov/

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
• To evaluate the antiviral activity of PBI-0451	• Proportion of subjects below the limit of detection (LOD) for infectious SARS-CoV-2 on Day 3 of treatment by infectious virus assay (IVA) from mid-turbinate (MT) swab
Secondary Objectives	**Secondary Endpoint**
• To evaluate safety and tolerability of PBI-0451	• Number of treatment-emergent AEs, SAEs, discontinuations due to AEs, and Grade 3 or 4 laboratory abnormalities
• To evaluate clinical efficacy of PBI-0451 versus placebo through study Day 28	• Proportion of subjects with sustained symptom resolution through Day 28 • Time to sustained symptom resolution through Day 28 • Proportion of subjects with COVID-19 related hospitalization or death from any cause through Day 28 • Severity of targeted COVID-19 symptoms • Number of COVID-19 related medical visits other than hospitalization, including acute/critical care visits through Day 28 • Number of days in any hospital unit for treatment of COVID-19
• To evaluate the effect of PBI-0451 on SARS-CoV-2	• Presence of SARS-CoV-2 virus, viral RNA or viral antigen based on IVA, quantitative reverse transcriptase polymerase chain reaction (qRT-PCR), and rapid antigen test (RAT), as specified in the Clinical Virology Analysis Plan (CVAP)
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate SARS-CoV-2 resistance to PBI-0451	• Sequence analysis of the SARS-CoV-2 M^{pro} gene (nsp5) and M^{pro} cleavage sites

• To evaluate SARs-CoV-2 resistant variant susceptibility to PBI-0451	• Susceptibility analysis of SARS-CoV-2 variants with M^{pro} amino acid substitutions and variants with substitutions in M^{pro} cleavage sites in the SARS-CoV-2 polyprotein
• To evaluate the relationship between SARS-CoV-2 detection methods	• Correlation of SARS-CoV-2 detection by IVA, RAT, and qRT-PCR, as specified in the CVAP
• To evaluate the incidence of rebound SARS-CoV-2 infection	• Proportion of subjects with clinical and/or virologic rebound
• To evaluate PBI-0451 PK	• PBI-0451 PK analysis from an intensive PK substudy of up to 50 subjects • PK parameters from sparse sampling of all subjects for population PK analysis

3. STUDY DESIGN

This protocol describes a Phase 2, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of PBI-0451 in nonhospitalized symptomatic adults with COVID-19 who are at standard risk of progressing to severe illness. Approximately 210 subjects will be randomized in the study.

An overview of the study design is provided in Figure 1.

3.1. Study Treatments

Following completion of screening and eligibility assessments, eligible subjects will be randomized 2:1 to 1 of 2 treatment groups on Day 1 as follows:

- PBI-0451: 2 × 350 mg tablets administered orally twice daily (BID) (1400 mg/day) with food for 5 days (10 total doses)
- Placebo: 2 × placebo to match PBI-0451 tablets administered orally BID with food for 5 days (10 total doses)

Randomization will be stratified as follows:

- SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization
- Received primary vaccination series, alone versus any booster shots
- PK substudy participation versus nonparticipation

3.2. Duration of Treatment

Eligible subjects will begin treatment immediately following randomization and completion of Day 1 assessments (first daily dose) and with the evening meal on Day 1 (second daily dose); subjects will continue BID dosing for a total of 5 days (10 total doses).

3.3. Discontinuation Criteria

Study drug will be discontinued in the following instances:

- Unacceptable toxicity, or toxicity that, in the judgement of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the subject's best interest
- Subject request to discontinue for any reason
- Pregnancy during the study (see Appendix 3)
- Concurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree

- Subject noncompliance
- Discontinuation of the study at the request of Pardes, a regulatory agency, or an institutional review board (IRB) or independent ethics committee (IEC)
- Subjects develop severe or critical COVID-19 illness defined as sustained pulse oximetry <94%, a respiratory rate of >30 breaths/min or dyspnea that requires medical attention

Subjects who discontinue study drug are encouraged to continue participation in the study for safety follow up. Subjects can discontinue participation at any time.

3.3.1. Rescue Therapy for Discontinuation

Subjects who experience severe COVID-19 illness (defined in this study as sustained pulse oximetry <94%, a respiratory rate of >30 breaths/min, or dyspnea that requires medical attention) should discontinue study drug and be immediately referred by the Investigator to emergency care or treated by the Investigator for standard of care treatment of symptoms including, but not limited to, other antivirals, supplemental oxygen, corticosteroids, Janus kinase inhibitors, or interleukin-6 blockers, in accordance with the NIH Treatment Guidelines (NIH 2022). The subject should continue participation in the study, with study drug discontinued, for safety follow-up and clinical outcome of the medically attended visit.

3.4. End of Study

The end of this study will be the last subject's last observation (or visit) up to Week 24.

3.5. Source Data

The source data for this study will be obtained from electronic data capture (EDC), central laboratory, local laboratory, specialty laboratory (for PK and/or ECG data).

3.6. Biomarker Samples for Optional Future Research

The following biological specimens will be collected from all subjects who have provided consent to participate in this study, and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including AEs) and/or dosage selection, and to better understand the biological pathways, biology of SARS-CoV-2 or related diseases caused by other CoVs, and/or the validation of a companion diagnostic for COVID-19 or PBI-0451. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to prospectively specify all tests that may be done on the specimens provided. The specific analyses will include, but may not be limited to, the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests that are no longer indicated and/or to add new tests based upon new state-of-the-art knowledge.

- Biological samples (blood and urine) will be collected relative to dosing (if applicable) to measure biomarkers with corresponding PK time points.

- Mid-turbinate (MT) nasal swabs will be collected to measure SARS-CoV-2 using qRT-PCR, IVA, RAT, and viral sequencing. Saliva samples will be collected to measure SARS-CoV-2 using qRT-PCR and IVA.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements.

3.7. Biomarker Sample for Optional Genomic Testing

In addition to the study-specific informed consent to be signed by each subject participating in the study, subjects will be offered to document agreement to provide additional blood sample for optional genomic research. The sample will be obtained from subjects who agree to participate and provide their additional specific consent.

A blood specimen will be collected for the evaluation of immune biomarkers that could regulate or be involved in the disposition of SARS-CoV-2 or PBI-0451. This sample will be collected at baseline/Day 1 prior to administration of the first dose of study drug but may be collected at any time during the study, if necessary.

The specimen collected for optional future genomic research may be used to advance the development of the drug and/or increase our knowledge and understanding of the biology of the disease under investigation or related diseases. This specimen may also be used to study the association of biomarkers with biological pathways, disease pathogenesis, progression, and/or treatment outcomes, including efficacy, AEs, and the processes of drug absorption and disposition. In addition, the specimen may be used to develop biomarker and/or diagnostic assays and establish the performance characteristics of these assays. The collection and analysis of optional genomic research specimens may facilitate the design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

The samples collected for optional genomic research will be destroyed no later than 15 years after the end of study or per country requirements.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A total of 210 subjects will be randomized in the study. Subjects are nonhospitalized, symptomatic males and nonpregnant, nonlactating females 18 to < 65 years of age with a positive direct test of SARS-CoV-2 infection (antigen based or nucleic acid amplification test [NAAT]) who are not at high-risk of progressing to severe disease.

4.1.1. Subject Replacement

Subjects who prematurely discontinue the study due to adverse events will not be replaced.

4.2. Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for participation in this study:

1. Can understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of any study procedures
2. Onset of COVID-19 symptoms ≤ 5 days prior to randomization with a positive SARS-CoV-2 test ≤ 24 hours prior to randomization. Authorized NAAT or antigen tests that detect viral RNA or protein, respectively, are allowed
3. Received primary vaccination series as defined by Centers for Disease Control and Prevention (CDC). Subjects should be advised during informed consent that alternate therapies may be available outside of study participation.
4. ≥ 2 symptoms of acute COVID-19 infection as determined by the investigator from the symptoms listed on the COVID-19 symptoms questionnaire present at randomization
5. Male and nonpregnant, nonlactating female subjects 18 to < 65 years of age. Females must have a negative serum or urine pregnancy test at screening and prior to the first dose of study drug unless permanently sterile or in a postmenopausal state (see Appendix 3)
6. Male and female subjects and/or their heterosexual partners must either be of nonchildbearing potential or must use effective contraception from screening through 90 days after the last dose of study drug (see Appendix 3)
7. Female subjects must refrain from egg donation and in vitro fertilization during treatment and for ≥ 28 days after the last dose of study drug
8. Male subjects must refrain from sperm donation from screening through 90 days after the last dose of study drug
9. Normal 12-lead ECG evaluation without clinically significant abnormalities

10. Able and willing to comply with all study requirements

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not eligible to participate in this study:

1. Considered at high-risk of developing severe illness from COVID-19 defined as ≥ 1 CDC underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (see Appendix 5)
2. Unvaccinated against SARS-CoV-2 (defined as having not completed a primary vaccination series)
3. Any SARS-CoV-2 vaccination within 3 month prior to randomization or anticipated to receive a SARS-CoV-2 vaccination (including a booster) during the 28-day study period
4. Currently hospitalized or expected to require hospitalization for COVID-19 within 48 hours of randomization
5. Currently being treated or expected to be treated for COVID-19 with monoclonal antibodies, convalescent serum, or direct-acting antiviral agents (all potential subjects should be informed of evolving treatment options during informed consent that alternate therapies may or may not be available to them outside of study participation)
6. Any clinical condition or laboratory result considered by the investigator to indicate any unstable or poorly controlled underlying clinically significant medical condition(s), active disseminated infection (other than SARS-CoV-2), or other medical condition that could represent a risk to the subject, including increasing the likelihood of a safety event, affect subject compliance, or affect efficacy and/or safety data collected during the 28-day study period
7. Known active liver disease, including nonalcoholic steatohepatitis/nonalcoholic fatty liver disease, chronic or active HBV or HCV infection, primary biliary cirrhosis, Child-Pugh Class B or C, chronic alcoholic liver disease, or acute liver failure
8. Receiving dialysis or having known severe renal impairment (chronic kidney disease, Stage 4 or above)
9. Unable or unwilling to comply with the protocol procedures
10. Participating in another interventional study with an investigational compound or device, including those for COVID-19
11. Known prior participation in this study or another study involving PBI-0451

12. Females who are pregnant or breastfeeding

13. Oxygen saturation of < 94% on room air

5. STUDY INTERVENTION AND CONCOMMITANT MEDICATIONS

5.1. Randomization, Blinding, and Procedures for Breaking Treatment Codes

5.1.1. Randomization

Subjects who meet eligibility criteria will be randomized in a 2:1 ratio to PBI-0451 or placebo and assigned a unique subject number via an interactive voice and web response system (IXRS) prior to initiation of dosing on Day 1. Randomization will be stratified as follows:

- SARS-CoV-2 positive direct test diagnosis ≤ 3 days (target 30%) versus > 3 days from first onset of COVID-19 symptom(s) ≤ 5 days prior to randomization
- Received primary vaccination series, alone versus any booster shots
- PK substudy participation versus nonparticipation

5.1.2. Blinding

The study is double-blinded. Subjects, investigators and all internal and external personnel directly involved in the conduct of the study will be blinded to treatment assignment. Study drug will be dispensed to subjects by the study pharmacist or designee in a blinded fashion.

Specified personnel may be unblinded based on their study role as follows:

- The statistician or designee in Biostatistics and/or Clinical Data Management who facilitates transfer of PK and/or virology sample logistics and data files between Pardes and vendors will be unblinded.
- Individuals in Clinical Packaging and Labeling or Clinical Supply Management who have an Inventory Manager role in the IXRS for purpose of study drug inventory management will remain unblinded.
- Individuals in Pharmacovigilance (PVE) responsible for safety signal detection, investigational new drug (IND) safety reporting, and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group-level summaries.
- Individuals in Clinical Virology responsible for monitoring for virologic rebound detection will be unblinded to individual case data. In particular, RAT and qRT-PCR data will be monitored on a per subject basis to trigger the request for confirmatory sample collection in the case of a potential virologic rebound.
- External (ie, contract research organizations [CROs]) biostatisticians and programmers will be unblinded for IND safety reporting.

- A select independent team that will not participate in any other study-related activities will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will be unblinded only at the study group level and will not have access to individual subject treatment assignment.

5.1.3. Procedures for Breaking Treatment Codes

In the event of a medical emergency for which breaking the blind is required to provide medical care to a subject, the investigator may obtain treatment assignment directly from the IXRS for that subject. Pardes recommends, but does not require, that the investigator contact the CRO medical monitor prior to breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine a subject's emergency medical care. The rationale for unblinding must be clearly explained in source documentation, along with the date on which the treatment assignment was unblinded. The investigator is requested to contact the CRO medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study. Therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will discontinue study treatment. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

5.2. Description and Handling of PBI-0451

5.2.1. Formulation

PBI-0451 350 mg tablets are modified oval tablets.

Refer to latest version of the IB for additional information.

5.2.2. Packaging and Labeling

PBI-0451 tablets are packaged in 20-count high-density polyethylene bottles with silica gel desiccant(s) and labeled "For Investigational Purposes Only".

Refer to the latest version of the IB for additional information.

5.2.3. Storage and Handling

PBI-0451 should be stored at controlled room temperature (15°C to 30°C [59°F to 86°F]) or as otherwise labeled.

Drug product should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, drug product should not be stored in a container other than the container in which it is supplied. Consideration should be given to handling, preparation, and disposal through measures that

minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure.

A sufficient quantity of PBI-0451 (and matching placebo tablets) to complete the study will be shipped to the investigator or qualified designee from Pardes or its designee.

Refer to the latest version of the IB for additional information.

5.3. Dosage and Administration

- PBI-0451: 2 × 350 mg tablets administered orally twice daily (BID) (1400 mg/day) with food for 5 days (10 total doses)
- Placebo: 2 × placebo to match PBI-0451 tablets administered orally BID with food for 5 days (10 total doses)

Subjects will take their first dose of study drug (PBI-0451 or placebo) with food as soon as possible after randomization, with the first dose designated as Day 1, and the second dose taken with the evening meal on Day 1 to ensure that a full total daily dose (1400 mg PBI-0451) is taken on the first day of treatment. Study drug will be taken with food, approximately 12 hours between doses, at approximately the same time for each BID dose for the remainder of 5 days of treatment.

5.4. Prior and Concomitant Medications

Concomitant use of certain medications or herbal/natural supplements and study drug may result in PK interactions resulting in increases or decreases in exposure of study drug or the medications.

The following medications are disallowed from screening through completion of study treatment. If a subject requires use of a disallowed medication, a request for such use must be reviewed by Pardes and, if approved, the subject may continue to participate in the study.

- Any and all illegal or illicit drug use (eg, amphetamines, cocaine, opiates), including use of prescription drugs outside the care of the prescribing physician
- Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance

5.5. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Each study site must keep accountability records that capture:

- The date received and quantity of study drug
- The date, subject number, and the study drug kit number dispensed

The date and quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

Pardes recommends that used and unused study drug supplies be destroyed at the site. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by CRO, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for the electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to CRO.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for disposal return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability.

6. STUDY PROCEDURES

The study assessments to be conducted for each randomized subject are presented in Table 1 and described in the following sections. The investigator must document any deviation from the protocol procedures and notify Pardes and CRO.

6.1. Informed Consent

Written informed consent must be obtained from each prospective subject before initiation of any screening procedure.

6.1.1. Consent for Optional Research

Subjects who provide additional, specific consent may provide additional samples for optional biomarker research as described in Section 3.7.

6.2. Subject Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that subjects are eligible to participate in the study prior to randomization and that subjects remain eligible for the duration of the study.

Once informed consent has been obtained, all screening tests and assessments have been conducted, and study eligibility has been confirmed, a subject will be randomized to receive PBI-0451 or placebo on Day 1. Up to 50 subjects at select sites who provide separate specific consent will participate in an intensive PK substudy.

Entry into screening does not guarantee enrollment into the study. To manage the total study enrollment, Pardes, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

6.3. Pretreatment Assessments

Screening assessments may be considered as baseline/Day 1 if the subject is eligible for the study and is randomized and receives the first dose of study drug on same day.

6.3.1. Screening Visit

Prospective subjects will be screened ≤ 5 days prior to randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history
- Complete physical examination, including vital signs, body weight, and height

- MT nasal swabs for SARS-CoV-2 RAT
- MT nasal swabs and saliva samples, as appropriate, for SARS-CoV-2 IVA, qRT-PCR, and sequence analysis
- Blood sample collection for the following analyses: serum pregnancy test (women of childbearing potential only, see Appendix 3)
- Serum/urine pregnancy test (females of childbearing potential only)
- 12-lead ECG
- Patient-reported outcomes (COVID-19 symptom questionnaire) and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility)
- Review of AEs and concomitant medications

From the time of obtaining informed consent through administration of the first dose of study drug, record all SAEs, as well as any AEs related to protocol-specified procedures on the Adverse Events electronic case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are considered medical history (see Section 7.2).

6.3.2. Baseline/Day 1 Assessments

Note: Screening assessments may be considered as baseline/Day 1 assessments if the subject meets eligibility requirements, is randomized, and receives the first dose of study drug on same day.

The following assessments will be completed on Day 1. The investigator must have received the results from either a direct SARS-CoV-2 antigen or qRT-PCR test and results from the serum/urine pregnancy test (females of childbearing potential only) and confirmed eligibility prior to randomization. Serology tests results for HIV, HBV, HCV and SARS-CoV-2 are not required for eligibility.

At the time of randomization, subjects will be assigned a unique subject number via the IXRS. The following study assessments must be completed prior to the administration of the first dose of study drug:

- Complete physical examination, including vital signs, and body weight
- MT nasal swabs for SARS-CoV-2 RAT
- MT nasal swabs and saliva samples, for SARS-CoV-2 IVA, qRT-PCR, and sequence analysis

- Testing for SARS-CoV-2 N-antibodies using the Roche Elecsys® Anti-SARS-CoV-2 assay
- Blood sample collection for the following analyses: hematology, chemistry, serology (HIV-1, HBV, HCV), coagulation panel, serum pregnancy test (women of childbearing potential only, see Appendix 3)
- Urine sample collection for urinalysis
- Creatinine clearance (CL_{CR}) (Cockcroft-Gault)
- Estimated glomerular filtration rate (eGFR, using Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2021)
- 12-lead ECG
- Biomarker sample for optional genomic testing
- Patient-reported outcomes (COVID-19 symptom questionnaire)
- Any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) since last study visit
- Optional household transmission survey
- Review of AEs and concomitant medications
- Dispense study drug for all 10 doses

Subjects will take their first dose of study drug with food immediately after randomization and completion of Day 1 assessments with the second dose taken with the evening meal on Day 1. The investigator will counsel subjects as to the importance of adherence to dosing and taking study drug at approximately the same times each day (see Section 5.3).

The following Day 1 assessments will occur after the subject has taken their first dose of study drug:

- Single PK sample
- Intensive PK sampling (substudy subjects only) (Note that the intensive PK sample may be collected at any study visit from Day 1 to 5.)

6.4. Treatment Assessments

During treatment, individual study visits must occur on separate calendar days within the visit window, with the time(s) of sample collection recorded.

Study procedures and assessments during treatment Days 2 to 5 are outlined in Table 1. Symptom-driven physical examination, including vital signs; sample collection for SARS-CoV-2 RAT, qRT-PCR, and IVA; and review of AEs and concomitant medications will occur at study visits on Days 2, 3, and 5.

Assessments on Day 5 will also include a single PK sample, an evaluation of "survival status" (see Table 1), completion of the optional household transmission survey, and sample collection for SARS-CoV-2 sequence analysis (if appropriate).

6.5. Posttreatment Assessments

Posttreatment study procedures and assessments at Days 10, 15, and 28 are outlined in Table 1.

Subjects who experience a relapse in symptom(s) after having no COVID-19 symptom(s) for ≥3 days or have a positive RAT (or clinic qRT-PCR test) after testing negative by RAT or qRT-PCR will be requested to return to clinic within 2 days for symptom-drive physical examination, vital signs, MT swab and saliva samples for RAT, IVA, qRT-PCR, and sequencing, household transmission survey, and review of AEs and concomitant medications.

A Week 24 follow-up assessment will be performed for all subjects (via telephone visit, virtual visit, or clinic visit, as convenient). Information regarding ongoing or recurrent COVID-19 symptoms, survival status, pregnancy status (for female subjects of childbearing potential and female partners of male subjects), and any hospitalizations or acute/critical care visits (eg, non-admitted hospital or other care facility) that have occurred since the last study visit will be collected.

6.6. Assessments for Early Discontinuation from Study

If a subject prematurely discontinues study drug, for example as a result of an AE, every attempt should be made to keep the subject in the study and continue to perform the required study-related procedures until stabilization per the investigator. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study and undergo an ET visit within 72 hours of permanently discontinuing the study drug as outlined in Table 1. Evaluations indicating abnormal results believed to be possibly or probably related to study drug at the ET visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline level, or is otherwise explained.

6.7. Pharmacokinetics Assessments

Plasma samples will be collected for measurement of PBI-0451 concentrations and estimation of PK parameters (and metabolite**[**s**]**, as applicable). Some subjects will have PK assessed by sparse sampling and other subjects by intensive PK substudy.

Plasma collection for subjects participating in the intensive PK substudy may occur at any study visit from Day 1 (the first dose of study drug) to Day 5. Samples for the intensive PK substudy will be drawn at the following time points relative to PBI-0451 dosing:

Predose (≤ 5 minutes before dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and (optional) 10-12-hours postdose.

A single PK sample will be collected from all subjects at study visits at baseline/Day 1 (after the first dose of study drug) and Day 5

Any remaining PK samples will be stored in a plasma bank and may be used for exploratory assessments, such as metabolites, protein binding, endogenous markers of drug-drug interactions, biomarkers of host responsiveness, and other investigational experiments.

6.8. Safety Assessments

Safety will be evaluated throughout the study, including physical examinations, vital signs, 12-lead ECG, laboratory studies (hematology, coagulation panel, chemistry, urinalysis), and review of AEs. Refer to Table 1 for the schedule of assessments. Collection of any additional assessments for routine safety monitoring at additional time points is at the discretion of the investigator based on GCP.

6.8.1. Adverse Events/Concomitant Medications/Protocol Restrictions

Evaluation for AEs, review of concomitant medications, and review of protocol restrictions will occur as outlined in Table 1. Refer to Section 7 for information regarding AEs.

Concomitant use of certain medications or herbal/natural supplements and study drug may result in PK interactions resulting in increases or decreases in exposure of study drug or the medications.

Medications that are disallowed from screening through completion of study treatment are listed below. If a subject requires use of a disallowed medication, a request for such use must be reviewed by Pardes and, if approved, the subject may continue to participate in the study.

- Any and all illegal or illicit drug use (eg, amphetamines, cocaine, opiates), including use of prescription drugs outside the care of the prescribing physician
- Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance

6.8.2. Patient-Reported Outcomes

Subjects will complete the following daily self-reported outcomes as outlined in Table 1.

- COVID-19 symptoms questionnaire
- COVID-19 weekly questionnaire
- Hospitalizations or acute/critical care visits (eg, nonadmitted hospital or other care facility) that have occurred since the last study visit

6.8.3. Household Transmission Survey

Subjects may complete the optional household transmission survey of confirmed SARS-CoV-2 infections in subject's household members as outlined in Table 1. No specific identifying information will be collected.

6.8.4. 12-Lead Electrocardiogram Assessment

ECG assessments will be conducted throughout the study as outlined in Table 1. Subjects should rest quietly in the supine position for a minimum of 5 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete.

6.8.5. Physical Examination

Complete and symptom-driven physical examinations will be conducted throughout the study as outlined in Table 1. The complete physical examination conducted at screening will include the following assessments:

- A complete physical examination must include source documentation of general appearance, and the following body systems: head, neck, thyroid; eyes, ears, nose, throat, mouth, and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; neurological.

Medical History and Concomitant Medications

- Review medical history, including history of allergies, prior and current use of nicotine or nicotine-containing products, alcohol and illegal drug use, and prior (≤ 30 days) and current medication use.

6.8.6. Vital Signs

The schedule of vital signs assessments is provided in Table 1. Vital sign measurements include blood pressure, heart rate, respiration rate, pulse oximetry, and temperature and should be taken once subjects have been seated or in the supine position for a minimum of 5 minutes. A subject's position for measurement should remain consistent throughout the study.

6.8.7. Body Mass Index

Height and weight will be collected at screening for calculation of body mass index for inclusion criteria.

6.8.8. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 1.

6.8.8.1. Blood Samples

Blood samples will be collected for the following laboratory analyses:

- Hematology: Hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume
- Coagulation panel: D-dimer, prothrombin time, activated partial thromboplastin time and international normalized ratio
- Chemistry: alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, total protein, albumin, lactic acid dehydrogenase, creatine phosphokinase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (see below), glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × upper limit of normal)
- Serum pregnancy test (females of childbearing potential only)
- Serology (SARS-CoV-2 N-antibodies [using the Roche Elecsys® Anti-SARS-CoV-2 assay], HIV-1, HBV [hepatitis B serum antigen; hepatitis B core antibody], HCV [hepatitis C antibody, reflex to HCV RNA])

6.8.8.2. Urine Samples

Urine samples will be collected for urinalysis.

6.8.9. Creatinine Clearance and Estimated Glomerular Filtration Rate

Weight will be collected at Baseline/Day 1 to calculate CL_{CR} and eGFR.

- CL_{CR} (using the Cockcroft-Gault method based on serum creatinine and actual body weight as measured at screening):

$$\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} \left| (\times 0.85 \text{ for females}) \right| = CL_{CR} \text{ (mL/min)}$$

- eGFR (using CKD-EPI 2021) expressed as a single equation:

$$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1) \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012 \text{ [if female]}$$

where:
S_{cr} = serum creatinine in mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.241 (female) or -0.302 (male)
$\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0
$\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0
Age (years)

6.9. Virology Assessments

MT nasal swab and saliva samples for virology assessment will be collected throughout the study as outlined in Table 1. The following virologic analyses are planned:

- SARS-CoV-2 IVA: $TCID_{50}$ (infected Vero E6 cell immunoassay)
- SARS-CoV-2 sequence analysis (MT nasal swab only)
- SARS-CoV-2 RAT (lateral flow immunoassay; MT nasal swab only)
- SARS-CoV-2 qRT-PCR

6.10. Sample Storage

Stored biological samples may be used by Pardes or its research partner(s) for future testing to provide additional data to answer questions that relate to the main study (refer to Section 3.6). At the end of this study, these samples may be retained in storage by Pardes for a period up to 15 years. If subjects provide additional specific consent, residual PK samples will be destroyed no later than 15 years after the end of study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a study drug that does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3). Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures, such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations in which an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-specified procedure is not an AE but rather considered to be preexisting and should be documented as medical history.

Preexisting events that increase in severity or change in nature after study drug initiation or during study treatment or as a consequence of participation in the clinical study are considered AEs.

7.1.2. Serious Adverse Events

A SAE is defined as an event occurring at any time during the study that results in the following:

- Death
- A life-threatening situation (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction. Such events may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, and development of drug dependency or drug abuse.

7.1.3. Study Drugs and Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the drug product, counterfeit or falsified medicine, and pregnancy, regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration, or administration of a study drug while the study drug is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose; medication error with an AE; intercepted medication error; or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a subject.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product label (as it applies to the daily dose of the subject in question). In

cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing AE relationship to study drug using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship of an AE to a study procedure (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of the study procedure (eg, venipuncture).

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Division of AIDS Toxicity Grading Scale, Version 2.1. For each episode, the highest grade attained should be reported as defined in the grading scale (Appendix 4).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-specified procedures.

7.3.2. Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship to study drug, until Day 28, and report them on the eCRFs as instructed.

All AEs should be followed until resolution or until the AE is stable, if possible. Pardes may request that certain AEs be followed beyond the protocol-specified follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship to study drug or a protocol-specified procedure, that occur after a subject consents to participate in the study (ie, after signing the ICF) through study Day 28, must be reported on the applicable eCRFs and to the CRO PVE as instructed below in this section.

Any SAEs and deaths that occur after Day 28, and is deemed relevant to the use of study drug, should also be reported.

PPD NA PVE

Phone: +1 888 483 7729

Fax: +1 888 529 3580

Investigators are not obligated to actively seek SAEs after study Day 28; however, if the investigator learns of any SAEs that occur after Day 28, and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to CRO PVE.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug special situations that occur from study drug initiation through study Day 28 must be reported to CRO PVE (Section 7.4.2). AEs and SAEs resulting in SSRs must be reported in accordance with the AE and SAE reporting guidance.

7.3.5. Concomitant Therapy Reports

7.3.5.1. Concomitant Therapy Special Situations Report

Special Situations Reports (SSR) involving a concomitant therapy (not considered study drug) that occur after the subject first consents to participate in the study (ie, after signing the ICF) through study Day 28, must be reported to CRO PVE utilizing the paper SSR (Section 7.4.2.3).

7.3.5.2. Concomitant Therapy Report

Special situations involving concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the subject's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and transmit the SAE information to CRO PVE within 24 hours of the investigator's knowledge of the event from ICF signature through study Day 28.

- If it is not possible to record and transmit the SAE information electronically, record the SAE on the paper SAE reporting form and transmit to CRO PVE within 24 hours:

PPD NA PVE
Phone: +1 888 483 7729
Fax: +1 888 529 3580

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to CRO PVE.

7.4.1.2. Paper Serious Adverse Event Reporting Process

- All SAEs will be recorded on the SAE report form and transmitted by email or fax within 24 hours of the investigator's knowledge of the event to the attention of CRO PVE from ICF signature through study Day 28.

PPD NA PVE
Phone: +1 888 483 7729
Fax: +1 888 529 3580

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process for Study Drug

- Site personnel will record all special situation data on the applicable eCRFs and transmit the information to CRO PVE from study drug initiation through study Day 28.

- If for any reason it is not possible to record the special situation information electronically, record the special situation on the paper SSR form and transmit to CRO PVE:

PPD NA PVE
Phone: +1 888 483 7729
Fax: +1 888 529 3580

- If a special situation has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any special situation reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to CRO PVE.

- See Section 7.4.2.3 for instructions on reporting special situations with concomitant medications.

7.4.2.2. Paper Special Situations Reporting Process for Study Drug

- All special situations will be recorded on the SSR form and transmitted by email or fax within 24 hours of the investigator's knowledge of the event to the CRO PVE from study drug initiation through Day 28.

PPD NA PVE Phone: +1 888 483 7729
Fax: +1 888 529 3580

7.4.2.3. Reporting Process for Concomitant Medications

- Special situations that involve concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to CRO PVE utilizing the paper SSR form to:

PPD NA PVE Phone: +1 888 483 7729
Fax: +1 888 529 3580

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

- Special situations involving concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a concomitant medication, must be reported as AEs.

7.4.2.4. Pregnancy Reporting Process

- The investigator should report pregnancies in female study subjects and/or female partners of male subjects that are identified after initiation of study drug and throughout the study, including the posttreatment follow-up period, to CRO PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

PPD NA PVE Phone: +1 888 483 7729
Fax: +1 888 529 3580

- The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

- Any other premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to the CRO PVE.

- The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to CRO PVE using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to CRO PVE.

PPD NA PVE Phone: +1 888 483 7729
Fax: +1 888 529 3580

- Refer to Appendix 3 for pregnancy precautions, definition of female of childbearing potential, and contraceptive requirements.

7.5. Sponsor Reporting Requirements

Depending on relevant local legislation and regulations, including the applicable FDA Code of Federal Regulations, the European Union Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation and regulations, Pardes may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions, or SUSARs. In accordance with the European Union Clinical Trials Directive (2001/20/EC), Pardes or a specified designee will notify worldwide regulatory agencies and the relevant IEC(s) in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by CRO PVE using reference safety information specified in the IB or relevant local label, as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as AEs or SAEs as applicable. In addition, laboratory or other abnormal assessments (eg, ECGs, radiologic studies, vital signs) that are associated with signs and/or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a

syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Division of AIDS Toxicity Grading Scale, Version 2.1 (Appendix 4). AEs associated with laboratory abnormalities should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the CRO medical monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Severity of AEs should be recorded and graded according to the following:

- Grade 1 (Mild) clinical AE defined as mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated will continue with study participation.
- Grade 2 (Moderate) clinical AE defined as moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated will continue with study participation if interventions are not contraindicated and the investigator and medical monitor agree to continue.
- Grade 3 (Severe) clinical AEs defined as severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated will discontinue study drug administration and continue with study follow-up assessments.
- Grade 4 (Potentially Life-Threatening) clinical AEs are defined as potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability; and will discontinue study participation.
- Grade 5 indicates death.

Any questions regarding toxicity management should be directed to the CRO medical monitor.

7.8. Medical Monitoring

A team of medically qualified individuals, including but not limited to, the Sponsor and the CRO Medical Monitors, and the Drug Safety Consultant are responsible for ongoing review of all AEs, concomitant medications, laboratory values (including virology), and vital signs (including

pulse oximetry), worsening of symptoms (COVID-19 symptom questionnaire, including dyspnea), acute/critical care visits (eg, nonadmitted hospital or other care facility), and study drug discontinuations, at a minimum monthly basis throughout the study, per the Safety Monitoring Plan. Serious adverse events (eg, hospitalizations, life threatening events, medically important events, deaths) will be evaluated by the Sponsor and the CRO Medical Monitor within 24 hours after being reported by the Investigator. Blinded study data will be evaluated for trends and any event which occurs in greater frequency will be evaluated for updating risk language and notifying the IRB and regulatory authorities, as required.

An independent select team that will not participate in any other study-related activities will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing (See Section 5.1.2), which may include, but not limited to, study termination or modification of the study to protect subject safety.

8. STATISTICAL CONSIDERATIONS

Summary statistics will be used to analyze the study data. Any statistical testing will be conducted to ensure that the overall alpha = 0.05 level (2 sided). Unless otherwise specified, data summaries and analyses will be reported by treatment group. Details of the statistical methods will be provided in the statistical analysis plan (SAP), including any deviations from the original planned analyses.

8.1. Analysis Objectives and Endpoints

The primary, secondary, and exploratory study objectives and endpoints are listed in Section 2.

8.2. Planned Analysis

8.2.1. Interim Analysis

An analysis of the primary and secondary endpoints will be conducted after 210 subjects complete the Day 28 study visit.

8.2.2. Final Analysis

The final analysis will be conducted after the last randomized subject has completed their Week 24 follow-up visit or discontinued the study, all outstanding data queries have been resolved, and the database has been cleaned and locked.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Enrolled Analysis Set

The all enrolled analysis set includes all subjects who sign the ICF. This is the primary analysis set for disposition.

8.3.1.2. Intention-to-Treat Analysis Set

The intention-to-treat (ITT) analysis set includes all randomized subjects. This is the primary analysis set for demographics and data listings.

8.3.1.3. Modified Intention to Treat Analysis Set

The modified intention-to-treat (mITT) analysis set includes all randomized subjects with ≥ 2 symptoms consistent with COVID-19 ≤ 5 days prior to randomization and a positive SARS-CoV-2 test (RT-PCR or RAT) ≤ 24 hours prior to randomization who received ≥ 1 dose of study drug. This is the primary analysis set for all clinical endpoints.

8.3.1.4. Modified Intent to Treat Virologic Analysis Set

The mITT virologic analysis set is a subset of the mITT analysis set that includes subjects who had detectable infectious SARS-CoV-2 by IVA at baseline/Day 1. This is the primary analysis set for the primary efficacy endpoint.

8.3.1.5. Safety Analysis Set

The safety analysis set includes all randomized subjects who received ≥ 1 dose of study drug. This is the primary analysis set for safety analyses.

8.3.1.6. Pharmacokinetics Analysis Set

The PK analysis set includes all subjects who participated in the intensive PK substudy and have ≥ 1 nonmissing PK concentration reported by the PK laboratory. This is the primary analysis set for PK analyses.

8.3.2. Data Handling Conventions

8.3.2.1. Missing Data

Missing data can have an impact upon the interpretation of the study data. As this study is of short duration, it is anticipated that missing data will be minimal. Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled. Any imputations of missing data will be described in the SAP.

8.3.2.2. Adjustments for Multiplicity

No adjustments for multiplicity are planned.

8.4. Demographic and Baseline/Day 1 Characteristics Analysis

Demographics (age, gender, race/ethnicity), and subject characteristics (SARS-CoV-2 Pango lineage, SARS-CoV-2 seropositivity, qRT-PCR, time since onset of symptoms) will be summarized by treatment group using descriptive statistics for the ITT analysis set.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of subjects below the LOD for infectious SARS-CoV-2 on Day 3 by IVA. For the primary endpoint, differences between PBI-0451 and placebo will be evaluated using stratum-adjusted Mantel-Haenszel proportions (adjusted for randomization strata). The proportion of subjects below the LOD for infectious SARS-CoV-2 at other time points will be summarized in a similar manner.

8.5.2. Secondary Analyses

The time to resolution of targeted COVID-19 symptoms will be estimated with the Kaplan-Meier method and summarized by treatment group. Differences between treatment groups will be determined using a Wilcoxon-Gehan test. The analysis of time to resolution of each targeted COVID-19 symptom will be conducted in a similar manner.

The proportion of subjects with COVID-19 related hospitalization or death from any cause will be summarized by treatment group. Differences between treatment groups will be assessed using Mantel-Haenszel proportions.

The number of COVID-19 related hospitalizations or acute/critical care visits and the number of days in any hospital unit for the treatment of COVID-19 will be summarized. Differences between treatment groups will be assessed using a van Elteren test stratified by the randomization factors.

SARS-CoV-2 viral load kinetics will be summarized by study visit. Differences between the treatment groups will be assessed with a van Elteren test stratified by the randomization factors.

SARS-CoV-2 clinical and virologic rebound will be summarized by the amount of viral RNA detected at baseline/Day 1, time to loss of clinical symptoms, time to negative RAT or IVA, and time to the first confirmed reappearance of symptoms and/or a positive RAT or qRT-PCR sample.

A correlation of the results of IVA, RAT, and qRT-PCR assessments will be evaluated.

8.6. Safety Analysis

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be determined from the study drug administration data. Exposure data will be summarized using descriptive statistics and listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. A treatment-emergent AE is defined as any AE that begins on or after the date and time of first dose of study drug up to the date of last dose of study drug plus 14 days. Treatment-emergent AEs, SAEs, and AEs leading to premature discontinuation of study drug/study will be summarized by treatment, system organ class, and preferred term.

Laboratory results and change from predose values for selected laboratory tests will be summarized by treatment at scheduled visits. The incidence of treatment-emergent laboratory abnormalities (Division of AIDS Toxicity Grading Scale) will be summarized by treatment.

By-subject listings of safety data will be provided.

8.6.3. Laboratory Evaluations

Listings of individual subject laboratory results will be provided. Selected laboratory data will be summarized using only observed data. Data and change from baseline/Day 1 at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined in the SAP. Incidence of treatment-emergent laboratory abnormalities, defined as values that increase ≥ 1 toxicity grade from baseline/Day 1 at any postbaseline time point up to and including the date of last dose of study drug plus 14 days will be summarized by treatment group. If baseline/Day 1 data are missing, any graded abnormality (ie, ≥ Grade 1) will be considered treatment emergent.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has discontinued study drug for ≥ 14 days will be listed.

8.6.4. Other Safety Evaluations

Vital signs and (safety) ECG data will be listed.

8.7. Pharmacokinetics Analysis

PBI-0451 plasma concentrations and PK parameters will be derived using noncompartmental methods (including metabolite[s] as applicable) and listed and summarized using descriptive statistics.

PBI-0451 plasma concentrations from the PK substudy and sparse sampling from the overall study population will be used in a population PK analysis and reported separately.

8.8. Sample Size

The sample size will be approximately 210 subjects to account for approximately 60% of randomized subjects who are anticipated to be SARS-CoV-2 negative by IVA at baseline/Day 1 and would be excluded from the mITT virologic analysis set. It should be noted that this sample size is sufficient with ≥ 80 power to detect a > 19% absolute difference in the proportion of subjects below the LOD for infectious SARS-CoV-2 virus (99% vs 81%) at Day 3 by IVA among subjects who had detectable infectious SARS-CoV-2 at baseline/Day 1. This assumes alpha = 0.05 and that 40% of subjects have detectable infectious virus at baseline/Day 1.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

Investigators should review all available treatment options for each individual potential subject, including those outside of this study, and risks associated with possibly receiving placebo with the potential subject. The Investigator should refer to the "NIH Treatment Guidelines" (NIH 2022), and the CDC "Interim Clinical Considerations for COVID-19 Treatment in Outpatients" and "Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals" to appropriately discuss the alternative options and risks for being in this study (CDC 2022). The potential subject should also be referred or receive a printout of the CDC "People with Certain Medical Conditions" and "COVID-19 Treatments and Medications" which includes language appropriate for the lay person regarding medical conditions attributed to a higher risk of severe COVID-19 and potential treatment (CDC 2022).

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Pardes or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Pardes or CRO of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or designated personnel as appropriate according to local regulations) will submit this protocol, the ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be

provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved ICF for documenting written informed consent. Each ICF (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative, the person conducting the consent discussion, and an impartial witness (if required by IRB/IEC or local requirements).

The ICF will inform subjects about genomic testing and/or planned sample retention. In addition to the study-specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples or to allow the use of the remainder of their already-collected specimens for optional future research, in accordance with applicable regulations. In addition to the study specific ICF to be signed by each subject participating in the study, subjects will be required to document agreement to provide additional samples for optional genomic research. The results of the tests done on the samples will not be given to the subject or the investigator.

9.1.5. Confidentiality

The investigator must ensure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Pardes, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions in accordance with local regulations. NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Pardes or its partner(s), including but not limited to the IB, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Pardes during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Pardes. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, IEC and government approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification
- Documentation that subject meets eligibility criteria (ie, medical history, physical examination, and confirmation of diagnosis) to support inclusion and exclusion criteria
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medication (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation if it occurs

All clinical study documents must be retained by the investigator for ≥ 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities

have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Pardes. The investigator must notify Pardes before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Pardes must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Pardes to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the EDC system. The eCRF casebook will capture only the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines (CCGs). Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or CRO staff who routinely review the data for completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries, as well as any changes to data fields, will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by CRO), the investigator will use his/her login credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, CRO will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to CRO's appointed study monitors, IRBs/IECs, and regulatory or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Pardes. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. Pardes will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Pardes in an abstract, manuscript, or presentation form or the study has been completed at all study sites for ≥ 2 years.
- The investigator will submit to Pardes any proposed publication or presentation along with the respective scientific journal or presentation forum ≤ 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Pardes's confidential information (see Section 9.1.5).
- The investigator will comply with Pardes's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Pardes will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Pardes/CRO may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the CRO medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Pardes/CRO access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both Pardes and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authority, and IRB/IEC. In terminating the study, Pardes/CRO and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

PARDES BIOSCIENCES, INC.
2173 SALK AVE SUITE 250
PMB #052
CARLSBAD, CA 92008

STUDY ACKNOWLEDGMENT

A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19

Amendment 1

26 August 2022

This protocol has been approved by Pardes Biosciences, Inc. The following signature documents this approval.

David Wilfret, MD

Name (Printed)
Vice President, Clinical Research

DocuSigned by:
David Wilfret
Signer Name: David Wilfret
Signing Reason: I approve this document
Signing Time: 8/26/2022 | 11:45:58 AM PDT
38A0AB01EBC046F2AE58BF0A858D4E5C

Signature

8/26/2022

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein, and I will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Pardes or its partner(s). I will discuss this material with them to ensure that they are fully informed about the drugs, the study, and the undertaking of confidentiality.

I agree that all information received from Pardes or its partner(s), including but not limited to the Investigator's Brochure, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Pardes during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written

consent from Pardes. I further agree to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

Principal Investigator Name (Printed)	Signature
Date	Site Number

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to subjects and sites:

    a) Subjects may be unable to return to the site to get the study drug, or the site may be unable to accept any subject visits. Without study drug, a subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: Study drug supplies may be provided to the subject from the site without a clinic visit, once it is confirmed that the subject may safely continue on study drug as determined by the investigator. A virtual study visit, via telephone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person subject visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study subjects if permitted by local institutional review board (IRB)/ independent ethics committee (IEC) as applicable and with Pardes's approval.

    b) Shipments of study drug could be delayed because of transportation issues. Without study drug, a subject would not be able to stay on the study drug as planned per protocol.

        Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify Pardes or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. Pardes will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

2) Subject safety monitoring and follow-up:

    a) Subjects may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

        Mitigation plan: For subjects who may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol, the Investigator or qualified delegate will conduct a virtual study visit, via telephone or video conferencing, to assess the subject within the target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

        i) Confirm if subject has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

iv) If applicable, confirm subjects study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed, it will be provided as described above in Item 1 above.

v) If applicable, remind subject to maintain current dosing and to keep all dispensed study drug kits for return at the next onsite visit.

b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories may be used as appropriate to monitor subject safety until the subject can return to the site for their scheduled visit per protocol. Any laboratory assessments conducted at a local lab due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local IRB/IEC and national laws and regulations. Remote consent will be allowed if has been approved by the local IRB/IEC. The consent process will be documented and confirmed by the normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur if scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required scheduled procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed subject visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out source data review or source data verification (SDV) or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or under-reporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. In compliance with CRO policy, a remote SDV should be arranged. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to subjects missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

      Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of PBI-0451 in study subjects remains unchanged.

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the subject is permanently sterile or has medically documented ovarian failure.

Females are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone level (FSH) is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy. Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless the subject is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

PBI-0451 is contraindicated in pregnancy because a malformation effect is unknown, taking into consideration class effects and genotoxic potential. PBI-0451 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, as there is limited safety information available to exclude the possibility of DDIs between PBI-0451 and hormonal contraception, hormonal contraception methods are not an acceptable form of contraception for female subjects participating in this study. Female subjects must use one of the highly effective contraceptive methods outlined below in Section 2.b.

Refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must also not rely on hormonal contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative pregnancy test on Day 1 prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter until the end of the contraception requirement.

Duration of required contraception for female subjects in this study is from screening and until 90 days after the last dose of study drug. Female subjects must agree to one of the following contraceptive methods:

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of one or more of the following methods of birth control:
  - Nonhormonal intrauterine device (IUD)
  - Bilateral tubal occlusion (upon medical assessment of surgical success)
  - Vasectomy in the male partner (upon medical assessment of surgical success)
  - Consistent and correct use of a double barrier method of contraception using two of the following barriers concurrently:
    - Male or female condoms (not to be used together)

    and

    - Female diaphragm ('cap')

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved. Local requirements of combining a single barrier method with either IUD or surgical sterilization are endorsed.

Female subjects must refrain from egg donation and in vitro fertilization during treatment and for ≥ 28 days after the last dose of study drug.

3) Contraception Requirements for Male Subjects

Male subjects must agree to use a male condom and an additional effective contraceptive method with their female partners, if their female partners are of childbearing potential (see Section 1.a), from treatment Day 1 until 90 days following the last dose of study drug. Effective methods of contraception for female partners of male subjects may include hormonal contraception or one of the methods outlined in Section 2.b.

Male subjects must refrain from sperm donation from screening throughout the study period and for at least 90 days following the last dose of study drug.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Female subjects will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from screening to 90 days after the last dose of study drug. Study drug must be discontinued immediately if pregnancy is confirmed during treatment.

Male subjects whose partner has become pregnant or suspects she is pregnant from screening to 90 days after the last dose of study drug must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.4.

Appendix 4. Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Please refer to Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 2.1 – July 2017)

Appendix 5. Modified Centers for Disease Control and Prevention: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19

The potential subject should be excluded from the study (exclusion criteria 1) if they have at least 1 underlying medical condition associated with increased risk for severe COVID-19 illness ("high-risk" and consequently increased risk of hospitalization and death) derived from the Centers for Disease Control and Prevention list of high-risk underlying conditions as outlined below and detailed at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

a. ≥65 years of age
b. Asthma
c. Active cancer
d. Cerebrovascular disease
e. Chronic kidney disease (if no history of CKD Stage 3 or above)
f. Chronic lung diseases limited to:
    i. Interstitial lung disease
    ii. Pulmonary embolism
    iii. Pulmonary hypertension
    iv. Bronchiectasis
    v. COPD (chronic obstructive pulmonary disorder)
g. Chronic liver diseases limited to:
    i. Cirrhosis (Child-Pugh A)
    ii. Non-alcoholic fatty liver disease
    iii. Alcoholic liver disease
    iv. Autoimmune hepatitis
h. Cystic fibrosis
i. Diabetes mellitus, Type 1 and Type 2
j. Disabilities

i. Attention-Deficit/Hyperactivity Disorder (ADHD)

ii. Cerebral Palsy

iii. Congenital Malformations (Birth Defects)

iv. Limitations with self-care or activities of daily living

v. Intellectual and Developmental Disabilities

vi. Learning Disabilities

vii. Spinal Cord Injuries

k. Heart conditions such as:

i. Heart failure

ii. Coronary artery disease

iii. Cardiomyopathies

l. HIV (human immunodeficiency virus)

m. Mental health disorders limited to:

i. Mood disorders, including depression

ii. Schizophrenia spectrum disorder

n. Neurological conditions limited to dementia

o. Obesity (BMI $\geq$30 kg/m^2)

p. Primary Immunodeficiencies

q. Solid organ or blood stem cell transplantation

r. Tuberculosis

s. Use of corticosteroids or other immunosuppressive medications

t. Immune deficiencies (except people with moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments)

Pardes Biosciences™

September 30, 2022

Re: A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19 (PBI-0451-0002)

Dear Investigator,

I am writing to make clarifications to the following sections of the PBI-0451-0002 protocol.

- Exclusion Criterion #8 in **Section 4.3: Exclusion Criteria**:

  Receiving dialysis or having known severe renal impairment (chronic kidney disease, Stage 4 or above)

  Contrary to Exclusion Criterion #8, Exclusion Criterion #1 excludes potential subjects who are:

  Considered at high-risk of developing severe illness from COVID-19 defined as ≥ 1 CDC underlying medical condition associated with an increased risk of developing severe illness from COVID-19 (see Appendix 5)

  Appendix 5 is a list of CDC underlying medical conditions associated with higher risk for severe COVID-19 and includes the following:

  - *Chronic kidney disease (if no history of CKD Stage 3 or above)*

  Subjects who have chronic kidney disease <u>Stage 3</u> or above are considered at higher risk of developing severe illness from COVID-19 and are therefore excluded from the study.

- Footnote g in **Table 1: Study PBI-0451-0002 Study Procedures Table** states:

  Mid-turbinate nasal swabs will be collected to measure SARS-CoV-2 using qRT-PCR, IVA, RAT, and viral sequencing. Saliva samples will be collected to measure SARS-CoV-2 using qRT-PCR and IVA. Parentheses indicate sample at ET visit if the subject discontinues treatment prior to Day 10.

  Footnote g in Table 1 stating "Day 10" is a typographical error. The parentheses indicate sample at the Early Termination (ET) visit for <u>SARS-CoV-2 IVA</u> only if the subject discontinues prior to <u>Day 15</u>.

Table 1. Study PBI-0451-0002: Study Procedures Table

	Screening[a] (Day -5 to Day 1)	Baseline/Day 1[b]	Day 2	Day 3	Day 5 (±1 day)	Day 10 (±2 days)	Day 15 (±2 days)	Rebound Ad Hoc Visit[d]	Day 28 (±3 days)	Week 24 Follow Up (±20 days)[e]	ET
Written Informed Consent	X										
Medical History	X										
Complete Physical Examination	X	(X)							X		X
Symptom-Driven Physical Examination			X	X	X	X	X	X			
Height	X										
Weight	X	(X)							X		X
Vital Signs[f]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 N-antibodies		X									
SARS-CoV-2 RAT[g]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 qRT-PCR Test[g]	X	(X)	X	X	X	X	X	X	X		X
SARS-CoV-2 Sequence Analysis[g,h]	X	(X)	(X)	(X)	X	(X)	(X)	X	(X)		(X)
SARS-CoV-2 IVA[g]	X	(X)	X	X	X	X	X	X			(X)
HIV-1, HBV (HbsAg and HbcAb), and HCV (HCV antibody reflex to HCV RNA) Testing		X									
12-Lead ECG	X	(X)			X	X			X		X
Optional Genomic Sample		X									
Hematology[i]		X			X	X			X		X

If you have any questions regarding the items discussed above or any other study-related issue, please reach out to your CRA.

Sincerely,

DocuSigned by:
David Wilfret
Signer Name: David Wilfret
Signing Reason: I approve this document
Signing Time: 9/30/2022 | 12:14:35 PM PDT
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David Wilfret, MD
Vice President, Clinical Research Development
Pardes Biosciences, Inc.

Administrative Letter #1

October 31, 2022

Re: Collection of saliva samples for Study PBI-0451-0002: A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19

Dear Investigator,

This Administrative Letter is about the collection of saliva samples for testing in the infectious virus assay (IVA) in Study PBI-0451-0002.

On 07 Oct 2022, Pardes Biosciences requested that all clinical sites quarantine the pre-filled cryovials (Lot No2203674-1) created for the collection of saliva samples for analysis of IVA due to a possible vial contamination indicated by discoloration and/or growth. These cryovials were prepared by DDL/Viroclinics Biosciences. The investigation at DDL in conjunction with Pardes into this issue is ongoing and provisions are being made for the return of the contaminated cryovials. The contamination issue is completely independent of Pardes operations and the investigational product, PBI-0451.

The initial observation of contaminated cryovials as well as an evaluation of study-related risks and mitigations addressing the issue were addressed by Pardes internally and is documented in a memo-to-file dated 14 Oct 2022, which is archived by the Pardes Quality department. Pardes Clinical Operation and PPD have informed all sites to quarantine the contaminated cryovials until provisions are made for their return to DDL.

The PBI-0451-0002 Study Team has been working diligently to re-supply all the study sites with a new lot of Saliva IVA sample collection cryovials. However, due to supply chain issues, it has been a challenge to ensure that all sites have the proper amount of Saliva IVA sample collection cryovials.

The purpose of this Administrative Letter for study PBI-0451-0002 is to inform all investigators and site personnel about a change in protocol for the continued collection of the SARS-CoV-2 Saliva IVA samples at Screening/Baseline, Day 2, Day 3, Day 5, Day 10, Day 15, Rebound Ad Hoc Visit, and Early Termination Visit (if prior to Day 15).

- Sites that have been re-supplied with the replacement batch of cryovials should continue to collect Saliva IVA samples as described in the protocol for Study PBI-0451-0002.
- Sites who have not yet received a replacement batch of cryovials should stop collecting Saliva IVA samples until they receive the replacement cryovials. These sites should continue to collect all other samples for virology testing (Rapid antigen test, mid-turbinate [MT] nasal swabs for IVA and qRT-PCR using the BD 3mL collection kits, and Saliva collection for qRT-PCR using the Omnigene kit) as described in the study protocol.
- Sites should resume collection of Saliva for IVA once they have been re-supplied with the new cryovials.

The primary endpoint in study PBI-0451-0002 will be assessed based on the detection of infectious virus from the MT nasal collections, not the saliva collections. Therefore, the MT swab for IVA must still be collected per protocol. Saliva IVA is an exploratory endpoint for this clinical trial and every effort should

be made to collect these samples, where possible. If it is not possible, then the missed samples will not be documented as a protocol violation.

Thank you for your partnership in this important clinical program for COVID-19. The modifications described in this Administrative Letter are considered non-substantial to the primary and secondary endpoints and non-critical (no impact to patient safety, patient care, nor data integrity). The full protocol will be amended to reflect this change at the next available opportunity.

As a reminder, all virologic samples must be shipped to arrive refrigerated at **DDL's processing lab** by World Courier within 36 hours of collection. Please do not ship any virologic samples to the PPD Central Lab. Please refer to the Collection Flow Chart (CFC) found in your lab manual for the full virology collection details.

If you have any questions regarding this or any other study-related concerns, please reach out to your PPD CRA directly.

Sincerely,

DocuSigned by:
David Wilfret
Signer Name: David Wilfret
Signing Reason: I approve this document
Signing Time: 10/31/2022 | 2:16:26 PM PDT
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David Wilfret, MD
Vice President, Clinical Research
Pardes Biosciences, Inc.

Pardes Biosciences™

Administrative Letter #2

November 17, 2022

Re: Collection of Saliva Samples for Infectious Virus Assay in Study PBI-0451-0002: A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19

Dear Investigator,

The purpose of this Administrative Letter #2 for Study PBI-0451-0002 is to inform all investigators and site personnel about a change in study procedures for stopping collection of the SARS-CoV-2 saliva samples for infectious virus assay (IVA) at all study visits (Screening, Baseline/Day 1, Day 2, Day 3, Day 5, Day 10, Day 15, Rebound Ad Hoc Visit, and Early Termination Visit [if prior to Day 15]). **All sites should stop collecting saliva samples for IVA immediately (saliva samples for qRT-PCR should continue to be collected).** The exploratory endpoint of correlation of SARS-CoV-2 detection by IVA from saliva samples will no longer be evaluated.

As communicated in Administrative Letter #1, the availability of pre-filled 5 mL UTM cryovials created for the collection of saliva samples for the IVA continues to be impacted by contamination and supply chain issues. Due to ongoing challenges in supply logistics, we are unable to source viable cryovials for this assay.

The following collection materials for the saliva IVA should be destroyed immediately:

1. SalivaBio kits (saliva collection aid)
2. Pre-filled 5 mL cryovials with 1.5 mL UTM
   a. Lot No. 2203674-2
   b. Lot No. G9999-647/648
3. "SARS-CoV-2 IVA Saliva" label

Pre-filled cryovials should be treated as a biohazard for the purposes of destruction. Prior to destruction, please record the quantities and lot numbers of the items destroyed.

The following IVA Saliva collection materials should be placed in quarantine immediately and returned to DDL (instructions for return will be forthcoming):

1. Pre-filled 5 mL cryovials with 1.5 mL UTM
   a. Lot No. 2203674-1

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Sites should continue to collect all other samples for virology testing as described in the study protocol:

- MT nasal swabs for rapid antigen test
- MT nasal swabs for IVA and qRT-PCR using the BD 3 mL collection kits
- Saliva for qRT-PCR using the Omnigene kit

As a reminder, **all virologic samples must be shipped refrigerated to DDL's processing lab by World Courier on the day the samples are collected (do not ship any virologic samples to the PPD Central Lab).** Please refer to the Collection Flow Chart found in your laboratory manual for the full virology collection details.

Thank you for your partnership in this important clinical program for COVID-19. The modifications described in this Administrative Letter are considered non-substantial to the primary and secondary endpoints and non-critical (no impact to patient safety, patient care, nor data integrity). The full protocol will be amended to reflect this change at the next available opportunity.

If you have any questions regarding this or any other study-related concerns, please reach out to your PPD CRA directly.

Sincerely,

DocuSigned by:
David Wilfret
Signer Name: David Wilfret
Signing Reason: I approve this document
Signing Time: 11/17/2022 | 11:30:09 AM PST
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David Wilfret, MD
Vice President, Clinical Research
Pardes Biosciences, Inc.

Pardes Biosciences™

February 10, 2023

Re: A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19 (PBI-0451-0002)

Dear Investigator,

The purpose of this letter is to clarify the following sections of the PBI-0451-0002 protocol regarding the unblinding of the study for the planned interim analysis after all subjects have completed the Day 28 study visit and the reporting of safety events.

- Section 5.1.2, Blinding, defines the study blinding for the clinical trial and specifies those instances and/or personnel who may require unblinding during study conduct prior to the interim analysis.
- Section 8.2.1, Interim Analysis, defines that a planned interim analysis of the primary and secondary endpoints will be conducted after 210 subjects complete the Day 28 study visit.
- Section 7.3, Investigator Reporting Requirements and Instructions, states that safety information, including Adverse Events (Section 7.3.2) and Serious Adverse Events (Section 7.3.3), is collected through Day 28, unless an SAE or death after Day 28 is deemed relevant to the use of study drug.

Therefore, the Study PBI-0451-0002 unblinding to occur as part of the planned interim analysis as defined in Section 8.2.1 is separate and unique from the reference to potential and unplanned unblinding prior to Day 28 referenced in Section 5.1.2, which has not occurred.

Treatment codes will be shared with Investigators following the Final Analysis, defined in Section 8.2.2, once the last randomized patient has completed the Week 24 follow-up visit or discontinued the study, and as a point of procedure, after the final database has been cleaned and locked.

If you have any questions regarding the items discussed above or any other study-related issue, please reach out to your CRA.

Sincerely,

DocuSigned by:
David Wilfret
Signer Name: David Wilfret
Signing Reason: I approve this document
Signing Time: 2/15/2023 | 1:43:49 PM PST
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David Wilfret, MD
Vice President, Clinical Research
Pardes Biosciences, Inc.

April 10, 2023

Re: A Phase 2 Double-blind, Randomized Study to Evaluate the Antiviral Activity, Safety, and Efficacy of Orally Administered PBI-0451 Compared with Placebo in Nonhospitalized Symptomatic Adults with COVID-19 (PBI-0451-0002)

Dear Investigator,

Attached, please find the Pardes Biosciences press release dated Monday, 03 April 2023, which announces the top-line results from the Phase 2 clinical trial PBI-0451-0002 evaluating pomotrelvir (PBI-0451) for the treatment of COVID-19. In summary, pomotrelvir did not meet the primary endpoint measured by the proportion of participants below the limit of detection for infectious SARS-CoV-2 on day 3 of treatment with pomotrelvir versus placebo.

Based on these results, Pardes is suspending further clinical development of pomotrelvir and is notifying you, effective 14 April 2023, that clinical trial PBI-0451-0002 is terminated per protocol Section 9.3.4, where Pardes has the right to terminate the study at any time. Participants who have not completed the Week 24 questionnaires by 14 April 2023 will not have this data collected as development of pomotrelvir is currently suspended. Terminating the clinical trial and not collecting all Week 24 questionnaires poses no risk to participant safety as all adverse event collection completed on Day 28 of the clinical trial assessments and all participants have completed the contraception requirement window.

Your CRA will contact you regarding study closeout procedures and treatment codes will be shared with all of the Investigators following final database lock.

If you have any questions regarding the items discussed above or any other study-related issues, please reach out to your CRA.

Sincerely,

DocuSigned by:
David Wilfret
Signer Name: David Wilfret
Signing Reason: I approve this document
Signing Time: 4/7/2023 | 11:42:13 AM PDT
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David Wilfret, MD
Vice President, Clinical Research
Pardes Biosciences, Inc.

Link to Press Release: https://ir.pardesbio.com/news-releases/news-release-details/pardes-biosciences-announces-top-line-results-phase-2-trial

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