Protocol Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effects of EDP-235 in Non-hospitalized Adults with Mild or Moderate COVID-19
Protocol Number:	EDP 235-101
Protocol Version and Date:	Version [redacted], 13 February 2023
Compound:	EDP-235
Study Phase:	2
Sponsor:	Enanta Pharmaceuticals, Inc. 500 Arsenal St. Watertown, MA 02472

[redacted]

SPONSOR SIGNATORY

Study Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effects of EDP-235 in Non-hospitalized Adults with Mild or Moderate COVID-19
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[redacted]

Enanta Pharmaceuticals, Inc.
500 Arsenal St.
Watertown, MA 02472

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines.

[redacted]

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LIST OF ABBREVIATIONS

3CLpro	SARS-CoV-2 3-chymotrypsin–like cysteine protease
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AUC_{tau}	area under the curve during the dosing interval
BMI	body mass index
C_{24}	concentration at 24 hours postdose
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
C_{trough}	trough plasma concentration (measured concentration at the end of a dosing interval)
CRO	contract research organization
CYP	cytochrome P450
DAIDS	Division of AIDS
DMC	Data Monitoring Committee
EC	ethics committee
EC_{90}	90% maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOFU	end of follow-up
EOS	end-of-study
EOT	end-of-treatment
[redacted]	
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCP	healthcare provider
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
[redacted]	
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	intensive care unit
IRB	institutional review board

IRT	interactive response technology
ITT-c	intent-to-treat
IWRS	Interactive Web Response System
LLON	lower limit of normal
LLOQ	lower limit of quantitation
LTFU	long-term follow-up
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Authorities
mITT	modified intent-to-treat
NP	nasopharyngeal
PCR	polymerase chain reaction
PE	physical examination
[redacted]	
PK	pharmacokinetic(s)
PP	per protocol
PRO	patient-reported outcome
QD	once daily
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing the time for ventricular depolarization
QTcF	QT interval corrected for heart rate according to Fridericia
RNA	ribonucleic acid
RR	interval between successive heartbeats using the R-wave peaks
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAF	safety (for the analysis population)
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCR	Screening
SoA	Schedule of Assessments
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TND	target not detected
ULN	upper limit of normal
VOC	variant of concern
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Enanta Pharmaceuticals, Inc.

Name of Investigational Product: EDP-235

Study Title: Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Effects of EDP-235 in Non-hospitalized Adults with Mild or Moderate COVID-19

Protocol Number: EDP 235-101

Phase of Development: 2

Number of Participants Planned: Approximately 200 participants will be randomized.

Planned Study Population: Male and female non-hospitalized participants aged from 18 to 64 years, inclusive, who have mild or moderate COVID-19.

Investigational Product, Dosage, and Mode of Administration: EDP-235 will be supplied as [redacted] capsules for oral administration. Participants will receive EDP-235 [redacted], EDP-235 [redacted], or placebo administered once daily [QD] for 5 days.

Duration of Treatment: 5 days

Objectives	Endpoints
Primary Objective • To evaluate the safety and tolerability of EDP-235	**Primary Endpoint** • Safety and tolerability of EDP-235 compared to placebo as assessed by, but not limited to, adverse events (AEs), clinical laboratory results, and vital signs through Day 33
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of EDP-235 on COVID-19 clinical symptoms and outcomes	• Time to improvement of targeted COVID-19 signs/symptoms using the COVID-19 Symptom Diary through Day 33 • Proportion of participants with targeted COVID-19 signs/symptom improvement using the COVID-19 Symptom Diary through Day 33 • Change from baseline in targeted COVID-19 signs/symptom score using the COVID-19 Symptom Diary through Day 33 • Proportion of participants with medically attended visits for COVID-19 through Day 33 • Proportion of participants requiring hospitalization (defined as ≥24 hours of acute care) for COVID-19 through Day 33 • Proportion of participants who require hospitalization and mechanical ventilation (invasive and non-invasive) through Day 33 • All-cause mortality through Day 33 • Proportion of participants with any of the following COVID-19 related events or all-cause mortality through Day 33 o complications based on the investigator's assessment o medically attended visits o hospitalizations o intensive care unit (ICU) admissions

	○ requirement for supplemental oxygen or increased in supplemental oxygen requirement ○ requirement for mechanical ventilation (invasive and non-invasive)
• To evaluate the effect of EDP-235 on SARS-CoV-2 viral load	• Change from baseline in SARS-CoV-2 RNA levels relative to placebo through Day 5 • Change from baseline in SARS-CoV-2 RNA viral load through Day 14 • Change from baseline in infectious SARS-CoV-2 viral load through Day 14 • AUC of SARS-CoV-2 RNA viral load through Day 14 • Proportion of participants with SARS-CoV-2 RNA viral load <lower limit of quantitation (LLOQ), target not detected (TND) over time through Day 14 • Time to SARS-CoV-2 RNA <LLOQ, TND through Day 33
• To evaluate the pharmacokinetics of EDP-235	• Plasma concentrations of EDP-235
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

Study Design:

This is a randomized, double-blind, placebo-controlled, parallel group, multi-site study in non-hospitalized adult patients who test positive for SARS-CoV-2 and have COVID-19 symptom onset within 5 days of randomization and who are not at high risk for progression to severe COVID-19.

Participants can be vaccinated or unvaccinated for COVID-19. Participants with prior COVID-19 infection <90 days before enrollment and/or who received any COVID-19 vaccine dose <90 days before enrollment are excluded from trial participation.

The study is composed of 4 periods:

- Screening period (D-1 to D1): Screening will occur within a 24-hour period between time of signing the informed consent and time of randomization (for those participants meeting study criteria).
- Treatment period: The treatment period will begin with the first dose of study drug on Day 1 and will conclude with the end-of-treatment (EOT) visit on Day 5.
- Follow-up period: The follow-up period will begin following the last dose of study drug and will conclude at the end of follow-up (EOFU) visit on Day 33.
- Long-term follow-up period (LTFU): The LTFU will begin at Day 34 and will concludes at the end-of-study (EOS) visit at Week 24.

The study duration for each participant is up to 24 weeks.

The design of the study is shown in Section 1.2. Study procedures are detailed in the Schedule of Assessments (SoA; Section 1.3).

Statistical Methods: The primary endpoint of the study is safety and tolerability of EDP-235 compared to placebo as assessed by, but not limited to, AEs, clinical laboratory results, and vital signs. All safety parameters will be analyzed descriptively. Safety analyses will be based on the Safety Population, defined as all randomized participants who receive at least one dose of double-blind investigational product. Analysis for the primary objective will be conducted after all randomized subjects complete the EOFU visit.

Analyses of clinical efficacy and antiviral activity will be based on the Intent-to-Treat (ITT-c) Population, defined as all participants in the Safety Population with their positive SARS-CoV-2 status confirmed by a central RT-PCR viral load at baseline >LLOQ and with at least one post-baseline primary efficacy measurement. An analysis of covariance (ANCOVA) model, with treatment group, serostatus (i.e., seropositive or seronegative), stratification factors, ie, age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤ 3 days or >3 days and ≤5 days), as factors, and baseline score as the covariate, will be used for treatment comparisons. Time to improvement of targeted COVID-19 signs/symptoms through Day 33 will be summarized graphically using Kaplan-Meier plots and analyzed

by the Cox proportional hazard model. The proportion of participants demonstrating targeted COVID-19 signs/symptoms improvement through Day 33 will be summarized.

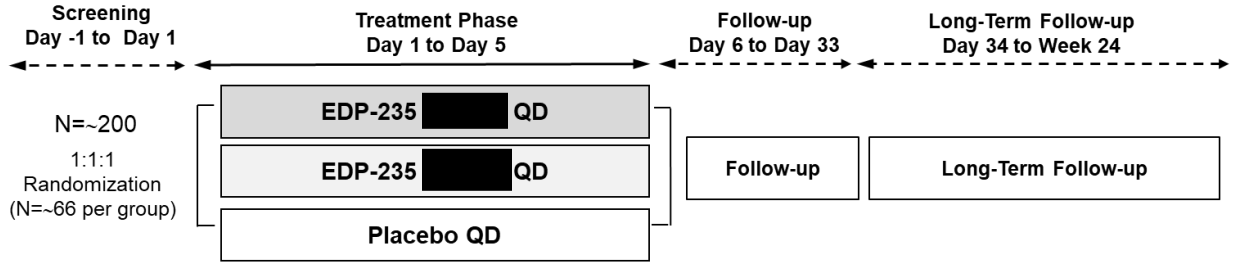
Plasma pharmacokinetic (PK) data concentration will be analyzed descriptively. PK analyses will be based on the PK population, which is defined as all participants in the Safety Population who receive active study drug and have measurable plasma concentration of study drug at any timepoint.

[redacted]

Sample size: Approximately 200 participants are planned. This sample size was selected to provide adequate safety data and evaluation of antiviral activity, PK, and clinical efficacy endpoints.

Data Monitoring Committee: Safety data will be reviewed by an independent Data Monitoring Committee (DMC) throughout the study. The DMC will be headed by a DMC Chair and will include members who are independent from the Sponsor. Procedures for data review, including timing and potential outcomes, roles and responsibilities, and interactions with the Sponsor and contract research organization (CRO), will be governed by a separate DMC charter.

1.2. Study Schema



1.3. Schedule of Assessments

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth, H=home visit by trained health care provider)
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	
Eligibility															
Informed consent form	X												X*		Informed consent must be obtained before conducting any study specific assessments. *Participants who completed the study at the EOFU (Day 33) visit will be asked to participate in the long-term follow-up. If the participant agrees to participate, informed consent must be obtained for the long-term follow-up. Section 12.1.3 AEs, concomitant medications and therapies, and medically attended visits should be captured in the eCRF retrospectively for subjects who re-enter the study; data will be collected starting the next day after the participant completes the EOFU visit.
Inclusion/exclusion review	X	X													Section 4.1 and Section 4.2
SARS-CoV-2 diagnostic test	X														The SARS-CoV-2 diagnostic test should be a PCR or rapid antigen test approved for use in the country; PCR test is preferred. A test is required at Screening if a positive result from a SARS-CoV-2 diagnostic test performed as part of clinical care within 24 hours prior to randomization is not available. If an NP swab is collected for the SARS-CoV-2 diagnostic test, one swab from the left nostril will be collected. Section 8.1.1
Demographics	X														Section 8.1.2
Medical, smoking and COVID-19 disease history	X														Section 8.1.2
Prior medications and therapies	X														Section 8.1.3
Physical examination (PE)	X														Full PE at Screening. Subsequent PEs performed at the discretion of investigator will be targeted to new signs and symptoms, including specific assessments for any changes from previous status. Section 8.1.4

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth, H=home visit by trained health care provider)
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	
Weight, height, BMI	X														BMI=weight (kg)/height (m)^2. Section 8.1.5
Vital signs	X	X[d]		X		X		X		X		X[g]			Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, body temperature, and pulse oximetry. Vital signs will be measured after the participant has been supine for at least 5 minutes. If screening and randomization occur on different calendar days, vital signs should be repeated on D1 for baseline values. Section 8.3.1
Pregnancy test	X	X[d]										X			For female participants of childbearing potential. Urine test will be performed at Screening. On D1 and Day 33 (EOFU), blood will be collected for serum pregnancy test to be performed by central laboratory. The screening urine pregnancy test results will be used to qualify participants at study entry. Section 8.1.6
Randomization and Study Drug															
Randomization		X													Section 6.4
Dispense study drug and study supplies		X													Study supplies may include an electronic device to record COVID-19 Symptom Diary and other PRO assessments. Section 8.1.7
Study drug dosing		X*	X	X*	X	X*									*Study drug (EDP-235 or placebo) administered at approximately the same time every day (+ 1 hour) at the clinic on clinic visit days (D1, D3, and D5). If this is not possible, the participant should take the medication at home before the visit. Self-administered dosing date and time of study drug will be recorded in source based on participant recall. Section 6.1
Study drug accountability				X		X*						X*			Study drug accountability by capsule count will be completed by study staff. Section 6.2 and Section 6.3 * If a participant discontinues treatment before completing 5 days of dosing but remains in the study, the participant should return study drug for accountability at the EOT visit. If a participant withdraws from the study before day 5, the participant

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth, H=home visit by trained health care provider)
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	
															should return study drug for accountability at the EOFU visit.
Study Assessments															
Clinical laboratory assessments (chemistry, hematology, coagulation)		X[d]*		X		X		X		X		X[g]			*Blood samples for select laboratory assessments should be taken from all randomized subjects and sent to the local laboratory for these identified tests (noted with superscript "a" in Table 1), which should be assayed and reported in an expedited manner. Review of laboratory results is not required prior to randomization or dosing. In parallel, hematology, chemistry, and coagulation panels should be sent to the central laboratory with the other Day 1 samples. From D1 through D5, samples should be collected predose. See Section 1.4 for the list of laboratory assessments.
Follicle stimulating hormone		X[d]													Follicle-stimulating hormone should be tested in selected postmenopausal females. Section 8.1.6
12-lead ECG (resting)		X[d]				X				X		X[g]			Section 8.3.2
COVID-19 Symptom Diary	X	X[d]	X	X	X	X	X	X	X	X	X	X			The COVID-19 Symptom Diary will be completed by participants during Screening to determine eligibility and after randomization, predose on Day 1 as a baseline measurement. If Screening and Day 1 occur on the same calendar day, the Screening Diary entry will be used as the baseline measurement and a separate Day 1 Diary will not be collected. In addition, the diary will be completed once daily at the same time each day ±2 hours. Section 8.2.2
Global Impression Questions		X[d]	X	X	X	X	X	X	X	X	X	X	X	X[h]	Global impression questions include Return to Usual Health, Return to Usual Activities, [redacted], which will be answered every day from D 1 to D33 after the COVID-19 symptom diary is completed. Section 8.7.2.1
[redacted]															

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth, H=home visit by trained health care provider)
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	
NP swabs collection		X[d]		X		X		X		X		X	X	X	NP swab samples will be collected predose by a study nurse or other trained healthcare professional (HCP) at the clinic or the participant's home. Two NP swabs, one from the right nostril (primary and first to be collected) and one from the left nostril (back-up) will be collected at each visit. Section 8.2.1
SARS-CoV-2 serology sample collection		X[d]										X			Serology tests are SARS-CoV-2 anti-spike and anti-nucleocapsid IgG and IgM antibodies. Section 8.7.1
Serum/plasma sample collection for exploratory research		X[d]				X				X		X	X	X	Exploratory biomarkers that will be evaluated include, but are not limited to, serum/plasma levels of SARS-CoV-2, C-reactive protein, D-dimer, troponin, high-sensitivity cardiac troponin, and absolute lymphocyte and neutrophil counts.. Section 8.7.1
■															
Assess ICU admissions, hospitalizations, and medically attended visits		Continuous from randomization through end of study participation													Medically attended visits include any unscheduled interactions with healthcare professionals other than study staff or designees that are not for routine health maintenance. Section 8.2.3
Adverse events	Continuous from signing of ICF through end of study participation[i]														Section 8.4
Concomitant medications and therapies	Continuous from signing of ICF through end of study participation														Concomitant medications and therapies will include the use of supplemental oxygen, increased use per PI judgment and mechanical ventilation. Section 8.1.3

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth, H=home visit by trained health care provider)
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	
PK sample collection		X+		X		X+*						X*			On D1, collect one postdose plasma PK sample at least 1 hr after dosing or right before the participant leaves the site, whichever is later. On D3 and D5, collect one plasma PK sample predose at the same approximate time as the NP swab collection. If the participant takes the study drug before the study site visit, a PK sample should be taken at the same approximate time as the NP swab collection. + On D1 and D5, intensive PK sampling will be conducted in a subset of participants. Additional PK samples will be drawn at 1, 2, 4, and 8 hours postdose. See Table 4 for time windows for intensive PK sampling. * If a participant discontinues treatment before D5 and remains in the study, a PK sample should be taken at the approximate time as the NP swab at the EOT Visit. If the subject discontinues treatment before D5 and does NOT remain in the study, a PK sample should be taken at the approximate time as the NP swab at the EOFU visit (Section 8.5).

Abbreviations: BMI=body mass index; D=day; ECG=electrocardiogram; EOFU=end of follow-up; EOS=end-of-study; EOT=end-of-treatment; ICF=informed consent form; LT=long-term; NP=nasopharyngeal; PGI-C: Patient Global Impression of Change; PGI-S: Patient Global Impression of Severity; PK=pharmacokinetic; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SCR=screening

[a] During the Follow-up period (Day 6 through Day 33), if the participant has symptom recurrence or symptom worsening, an unscheduled visit should be done within 2 days of patient reported symptom recurrence or worsening. At the unscheduled visit, NP swabs will be collected in addition to clinical assessments deemed necessary by the Investigator.

[b] Screening assessments should occur within 24 hours of randomization.

[c] D1 assessments are to be done only in randomized participants. Randomization, predose baseline measurements, and dosing must occur on the same calendar date.

[d] These assessments should be done predose as baseline measurements.

[e] Participants who discontinue treatment before completing 5 days of dosing should return to the study site within 24 hours of their last dose to complete EOT procedures and proceed to complete all follow up assessments 4, 9 and 28 days (EOFU visit) after their last dose of study drug. Participants who discontinue the study before Day 33 (EOFU) should return to the study site within 24 hours and no more than 48 hours later to complete the EOFU procedures.

[f] Visits may be completed at the study site or by study site personnel via a home visit, if feasible.

Period	SCR	Treatment					Follow-up[a]						LT Follow-up		Notes
Day	-1 to 1[b]	1[c] Rand.	2	3	4	5[e]	6 to 8	9 (±1d)	10 to 13	14 (±1d)	15 to 32	33 (±1d)[e]	Wk 12 (±7d)	Wk 24 (±7d)	
Visit Name	SCR	V1	T1	V2	T2	V3 EOT		V4		V5		V6 EOFU	V7	V8 EOS	(C=clinic, T=telephone call or telehealth, H=home visit by trained health care provider)
Type of Visit	C	C	T	C/H[f]	T	C/H[f]		C/ H[f]		C/ H[f]		C/H[f]	C/H[f]	C/H[f]	

[g] These assessments are only required for participants who discontinued the study before Day 5 (ie, do not have an EOT visit before discontinuing the study) or participants who discontinued the study after Day 5 and before Day 14. These participants should have an EOFU visit with additional assessments as indicated.

[h] For the Week 12 and Week 24 assessments, paper questionnaires may be used for the Global Impression Questions [redacted] and transcribed into the eCRF.

[i] At Week 12 and Week 24, study staff will ask each participant if they have COVID-19 signs and symptoms and record that information into the AE eCRF.

1.4. Laboratory Assessments

Table 1: Clinical and SARS-CoV-2 Laboratory Assessments

CHEMISTRY PANEL Alanine aminotransferase[a] Albumin, serum[a] Alkaline phosphatase, serum [a] Amylase[a] Aspartate aminotransferase[a] Bilirubin, total and direct[a] Blood urea nitrogen Blood urea nitrogen /creatinine ratio (calculation) Calcium, serum Creatine kinase Creatinine, serum[a] Glomerular filtration rate, estimated[b] Uric acid Electrolyte panel (sodium, potassium, chloride, bicarbonate)[a] Phosphorus Gamma glutamyl transferase Globulin, total Glucose, serum[a] Cholesterol Triglycerides Lactate dehydrogenase Lipase Protein, total serum	**COAGULATION PANEL** International normalized ratio[a] Prothrombin time[a] Activated thromboplastin time[a] **PREGNANCY AND OTHER ASSESSMENTS** Urine pregnancy test Serum pregnancy test (Day 1 only for central laboratory) Follicle-stimulating hormone **SARS-CoV-2 ASSESSMENTS** SARS-CoV-2 diagnostic test (nasal or nasopharyngeal secretions) SARS-CoV-2 RNA quantitation of viral load (nasopharyngeal secretions) SARS- CoV-2 infectious viral load (nasopharyngeal secretions) Respiratory pathogen panel (nasopharyngeal secretions) [redacted] SARS-CoV-2 RNAemia (plasma or serum) SARS-CoV-2 nucleocapsid antigenemia (plasma or serum) SARS-CoV-2 serology (anti-spike and anti-nucleocapsid antibodies; serum) [redacted]
HEMATOLOGY PANEL Hemoglobin[a] Hematocrit[a] Differential white blood cell count, percentage and absolute (basophils, eosinophils, lymphocytes, monocytes, neutrophils)[a] Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume Platelet count[a] Red blood cell count White blood cell count[a]	

[a] On Day 1, blood samples for these assessments should be collected and sent to the local laboratory for testing and reporting in an expedited manner. In parallel, all required samples as specified in the laboratory manual should be sent to the central laboratory.

[b] Estimated glomerular filtration rate will be calculated using the CKD-EPI equation.

2. INTRODUCTION

2.1. Overview

EDP-235 is a novel inhibitor of the SARS-CoV-2 3CL protease. This study will evaluate the safety, pharmacokinetics, antiviral activity, and clinical efficacy of EDP-235 in non-hospitalized, symptomatic adult participants with mild or moderate COVID-19.

2.2. Background

In December, 2019, reports of a series of pneumonia cases of unknown etiology emerged from Wuhan in the Hubei province of central China.[1] On January 7, 2020, Chinese health authorities reported that this cluster of cases was associated with a novel coronavirus, 2019-nCoV.[2] Based on the phylogenetic- and taxonomic-relatedness of 2019-nCoV to the human and bat severe acute respiratory syndrome coronaviruses (SARS-CoVs), the virus was designated SARS-CoV-2, and the resultant disease termed COVID-19.

With millions of confirmed cases and deaths worldwide, COVID-19 continues to represent a significant medical and social burden to the world community. Despite the availability of COVID-19 vaccines, direct acting antiviral agents and monoclonal antibodies for the treatment of COVID-19, there is still a need for highly effective antiviral therapies.

EDP-235 is a highly potent inhibitor of SARS-CoV-2 3CL protease (3CLpro), one of two cysteine proteases that are indispensable for SARS-CoV-2 replication. EDP-235 is a slow -onset, -slow reversible inhibitor of 3CLpro, with an IC_{50} (half-maximal inhibitory concentration) of 5.8 [redacted] nM. [redacted] Additional information about EDP-235 is available in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

EDP-235 exhibits slow-onset, slow-reversible binding to the target protein, is competitive with the peptide substrate, and is highly selective for the viral protease over host proteases. EDP-235 does not induce measurable cytotoxicity in any of the cell culture models used in these studies. EDP-235 is an orally administered antiviral agent targeting the SARS-CoV-2 3-chymotrypsin–like cysteine protease (3CLpro) enzyme. The 3CLpro enzyme represents an attractive antiviral target because it is essential in the viral replication cycle (ie, in processing viral polyproteins into functional units) and has a low likelihood of off-target activity, owing to the absence of recognized human analogues.

Study EDP 235-101 is the first trial to evaluate the safety, PK, antiviral activity and clinical efficacy, of EDP-235 in non-hospitalized adults with mild or moderate COVID-19; consequently, the efficacy and safety of EDP-235 in this population are not known. Because EDP-235 shares the same mechanism of action as nirmatrelvir, it is possible that participants in the present study may have a more rapid clearance of SARS-CoV-2 infection and a reduction in the symptoms associated with SARS-CoV-2 infection compared with those who do not receive

EDP-235. When nirmatrelvir was evaluated in standard-risk patients with COVID-19, although the primary efficacy endpoint of self-reported, sustained alleviation of all symptoms for 4 consecutive days, as compared to placebo, was not met, a 70% reduction in hospitalization and no deaths was observed in the treated population compared to placebo.[5] However, it is possible that no such effect will be observed. Additionally, participants randomized to the placebo treatment group will not be expected to derive any such benefit.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective • To evaluate the safety and tolerability of EDP-235	**Primary Endpoint** • Safety and tolerability of EDP-235 compared to placebo as assessed by, but not limited to, adverse events (AEs), clinical laboratory results, and vital signs through Day 33
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of EDP-235 on COVID-19 clinical symptoms and outcomes	• Time to improvement of targeted COVID-19 signs/symptoms using the COVID-19 Symptom Diary through Day 33 • Proportion of participants with targeted COVID19 signs/symptom improvement using the COVID-19 Symptom Diary through Day 33 • Change from baseline in targeted COVID-19 signs/symptom score using the COVID-19 Symptom Diary through Day 33 • Proportion of participants with medically attended visits for COVID-19 through Day 33 • Proportion of participants requiring hospitalization (defined as ≥24 hours of acute care) for COVID-19 through Day 33 • Proportion of participants who require hospitalization and mechanical ventilation (invasive and non-invasive) through Day 33 • All-cause mortality through Day 33 • Proportion of participants with any of the following COVID-19 related events or all-cause mortality through Day 33 o complications based on the investigator's assessment o medically attended visits o hospitalizations o intensive care unit (ICU) admissions o requirement for supplemental oxygen or increased in supplemental oxygen requirement o requirement for mechanical ventilation (invasive and non-invasive)
• To evaluate the effect of EDP-235 on SARS-CoV-2 viral load	• Change from baseline in SARS-CoV-2 RNA levels relative to placebo through Day 5 • Change from baseline in SARS-CoV-2 RNA viral load through Day 14

	• Change from baseline in infectious SARS- CoV-2 viral load through Day 14 • AUC of SARS-CoV-2 RNA viral load through Day 14 • Proportion of participants with SARS-CoV-2 RNA viral load <LLOQ, target not detected (TND), over time through Day 14 • Time to SARS-CoV-2 RNA <LLOQ, TND through Day 33
• To evaluate the pharmacokinetics of EDP-235	• Plasma concentrations of EDP-235
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

4. STUDY POPULATION

Approximately 200 participants are planned to be randomized into this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex

1. Male or female individuals who are 18 to 64 years of age, inclusive, at the Screening visit.

Type of Participant and Disease Characteristics

2. Tested positive for SARS-CoV-2 ≤24 hours before randomization by a diagnostic test approved for use in the country (PCR or rapid antigen test).
3. Initial onset of COVID-19 symptoms ≤5 days before randomization and at least 2 of the following signs/symptoms attributable to COVID-19 present and one of at least moderate severity at Screening as reported by the participant in the COVID-19 Symptom Diary: Stuffy or runny nose, sore throat, shortness of breath (difficulty breathing), cough, low energy or tiredness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, nausea.

Contraceptive Requirements

4. Female participants: Heterosexually active female participants of childbearing potential must agree to use 2 effective birth control methods for the duration of the study and for 30 days after the last dose of study drug (Section 4.5).
5. Male participants: Heterosexually active male participants and their female partners of childbearing potential must agree to use 2 effective birth control methods for the duration of the study and for 90 days after the last dose of study drug (Section 4.5).

Informed Consent

6. Capable of giving signed informed consent as described in Section 12.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other Inclusion Criteria

7. Willing and able to adhere to the study assessments, visit schedules, prohibitions, and restrictions, as described in the protocol.

4.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Prior SARS-CoV-2 infection <90 days before enrollment and/or received any COVID-19 vaccine dose <90 days before enrollment.
2. Has one or more conditions associated with high risk for severe COVID-19 (see list of conditions in Appendix 1).
3. History of hospitalization for the medical treatment of COVID-19.
4. Currently hospitalized or anticipated need for hospitalization in the clinical opinion of the investigator.
5. Known medical history of active liver disease (other than nonalcoholic hepatic steatosis), including chronic or active hepatitis B (defined as HBsAg-positive) or C (defined as detectable HCV RNA) infection, primary biliary cirrhosis, Child-Pugh Class A (mild hepatic impairment), B (moderate hepatic impairment) or C (severe hepatic impairment), or acute liver failure.
6. Receiving dialysis or have known moderate to severe renal impairment (ie., eGFR <60 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula).
7. Suspected or confirmed concurrent active systemic infection other than COVID-19 that may interfere with the evaluation of response to the study drug, as determined by the investigator.
8. Any comorbidity requiring hospitalization and/or surgery within 7 days before study entry, or that is considered life threatening within 30 days before study entry, as determined by the investigator.
9. Known HIV infection with a HIV viral load greater than 400 copies/mL or medication for HIV treatment that is prohibited in this study (Section 6.10) based on medical history within 6 months before the screening visit.
10. History of hypersensitivity or other contraindication to any of the components of the study drug, as determined by the investigator.
11. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior, laboratory abnormality or other finding that, in the opinion of the investigator, might confound the results of the study, pose an additional risk in administering study drug to the participant, could prevent, limit, or confound the protocol specified assessments, or deems the participant unsuitable for the study.

Prior/Concomitant Medications

12. Has received or is expected to receive pre-exposure prophylactic SARS-CoV-2 mAb.
13. Has received or is expected to receive convalescent COVID-19 plasma.

[redacted]

Diagnostic Assessments

[redacted]

16. Oxygen saturation of ≤93% on room air obtained at rest within 24 hours before randomization.

    Note: For a potential participant who regularly receives chronic supplementary oxygen for an underlying lung condition, oxygen saturation should be measured while on their standard home oxygen supplementation.

Prior/Concurrent Clinical Study Experience

17. Participating in another interventional clinical study with an investigational agent or device, including those for COVID-19, within 30 days or five half-lives of the agent, whichever is longer, before signing the ICF.

Other Exclusion Criteria

18. Females who are pregnant or breastfeeding.

4.3. Lifestyle Considerations

There are no lifestyle restrictions for this study.

4.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

4.5. Contraception Requirements

A woman of childbearing potential who is sexually active with a male must agree to use two effective methods of contraception from the date of Screening until 30 days after her last dose of study drug. Effective methods of contraception are defined as follows:

A condom for the male partner and at least one of the following for the female participant:

- Intrauterine device
- Oral, injectable, implantable, transdermal, or intravaginal hormonal contraceptive (Note: hormonal contraception must be associated with the inhibition of ovulation)

The above does not apply to 1) a female participant who has a vasectomized male partner provided that partner is the sole sexual partner of the participant, and the vasectomized partner has received medical assessment of surgical success, or 2) a female participant who is of nonchildbearing potential (ie, physiologically incapable of becoming pregnant) as defined below:

- Has had a partial or complete hysterectomy,
- Has had a bilateral oophorectomy (ovariectomy),
- Has had a bilateral tubal ligation or fallopian tube inserts, or
- Is postmenopausal (a total cessation of menses for at least 2 years; participants with a cessation of menses up to 2 years and a follicle stimulating hormone [FSH] level of >35 mIU/mL will also be considered to be postmenopausal.)

A male participant who has not had a vasectomy and is sexually active with a woman of childbearing potential must agree to use effective contraception from the date of Screening to 90 days after his last dose of study drug. Effective contraception is defined as a condom and at least one of the following for a female partner:

- Intrauterine device
- Oral, injectable, implantable, transdermal, or intravaginal contraceptive (Note: hormonal contraception must be associated with the inhibition of ovulation).

Male participants must agree to refrain from sperm donation from the date of Screening until 90 days after his last dose of study drug.

5. STUDY DESIGN

5.1. Overall Design

This is a randomized, double-blind, placebo-controlled, parallel group, multi-site study in non-hospitalized adult patients who have mild or moderate COVID-19 and COVID-19 symptom onset within 5 days of randomization.

Participants will be randomized in a 1:1:1 ratio to receive either EDP -235 [redacted], EDP-235 [redacted], or placebo orally once daily for 5 days. Randomization will be stratified by age (≤50 years or 51 to 64 years) and the duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days).

The study includes 4 periods:

- Screening period (D-1 to D1): Screening should occur within a 24-hour period between time of signing the informed consent and time of randomization (for participants meeting study entry criteria).
- Treatment period: The treatment period will begin with the first dose of study drug on Day 1 and will conclude with the end-of-treatment (EOT) visit on Day 5.
- Follow-up period: The follow-up period will begin following the last dose of study drug and will conclude at the EOFU visit on Day 33 (28 days after the last dose of study drug).
- Long-term follow-up period (LTFU): The LTFU period will begin on Day 34 and end at the end of study (EOS) visit at Week 24.

Participants meeting all study criteria and randomized into the study are considered enrolled.

Screening and Day 1 should occur at the study site as a clinic visit. All other visits may be completed at the study site or via a home visit, if feasible. The total duration of the study is 24 weeks.

Participants who completed the study at the EOFU (Day 33) visit will be asked to participate in the LTFU. If the participant agrees to participate, informed consent must be obtained for the LTFU. AEs, concomitant medications and therapies, and medically attended visits should be captured in the eCRF retrospectively for participants who re-enter the study; data will be collected starting the day after the participant completes the EOFU visit.

Safety data will be reviewed by an independent Data Monitoring Committee (DMC) throughout the study (see Section 9.4).

[redacted]

5.2. Scientific Rationale for Study Design

The novel SARS-CoV-2 coronavirus, which is responsible for COVID-19 disease, was first reported in Wuhan, China, in December 2019. The virus rapidly spread, and the World Health Organization declared a pandemic by March 2020. With millions of confirmed cases worldwide

and deaths, COVID-19 continues to represent a significant medical and social burden to the world community. Despite the availability of effective COVID-19 vaccines, the duration of immunity conferred by vaccine has varied considerably. Moreover, lifelong immunity is provided by neither natural infection nor vaccination. Furthermore, the emergence of variants and sub-variants with increased transmissibility and immune evasion capacity has been associated with new waves of infection worldwide.

Despite the availability of effective direct acting antiviral agents and monoclonal antibodies for the treatment of COVID-19, there is still a need for highly effective therapies. In one study, nirmatrelvir/ritonavir failed to demonstrate a clinical benefit with regards to self-reported, sustained alleviation of all symptoms in a pivotal phase 2/3 trial in standard risk patients.[5] Currently, no antivirals have received emergency use authorization (EUA) or approval for the treatment of COVID-19 in non-hospitalized patients at standard risk for severe disease. Therefore, this represents an unmet medical need. Antivirals that have received EUA for the treatment of mild to moderate COVID-19 in non-hospitalized subjects include nirmatrelvir/ritonavir, remdesivir and molnupiravir.

5.2.1. Justification of Study Design

Study EDP 235-101 aims to evaluate the safety, pharmacokinetics and antiviral activity and clinical efficacy of EDP-235 in outpatient participants with mild to moderate COVID-19 who are not at high risk of progression to severe COVID-19. To fully investigate the effects of EDP- 235, a double-blind, placebo-controlled study design was selected, where participants will be randomized 1:1:1 to receive either EDP-235 [redacted], EDP-235 [redacted], or placebo. Because the study will enroll only participants that are not at high risk for severe or critical COVID-19, and there is no EUA or approved treatments for this population, use of a placebo-controlled design is justified.

Early in the clinical course, COVID-19 is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this, it is anticipated that therapies that directly target SARS-CoV-2 would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19. Because the window for optimal intervention for SARS-CoV-2 infection may be limited, individuals are eligible for participation in the present study if their initial onset of COVID-19 symptoms is ≤5 days before randomization.

Symptom improvement over time will be assessed using a self-reported questionnaire, in line with regulatory guidance.[6] Given the risk for disease progression associated with SARS-CoV-2 infection, several secondary clinical endpoints will be evaluated, including but not limited to requirement for hospitalization, requirement for ICU care, and requirement for oxygen supplementation.

5.2.2. Rationale for Endpoints

5.2.2.1. Rationale for Primary Endpoint

The primary endpoint is the safety and tolerability of EDP-235 compared to placebo as assessed by, but not limited to, adverse events (AEs), clinical laboratory results, and vital signs. The

selection of the safety endpoints is appropriate to generate additional safety information in the patients with mild to moderate COVID-19 who are not high risk for progression to severe COVID-19. Treatment with antiviral agents targeting the chymotrypsin–like cysteine protease enzyme in patients with mild to moderate COVID-19 have yielded a similar safety and tolerability profile compared to placebo with regards to incidence of adverse events, grade 3 or 4 AEs, SAEs (1.6% vs. 6.6%), and adverse events leading to discontinuation of study drug.

5.2.2.2. Rationale for Secondary Endpoints

Secondary endpoints include those related to antiviral activity and clinical outcomes of COVID--19 and safety of EDP -235 treatment. The antiviral activity of EDP-235 on viral kinetics over 14 days including SARS-CoV-2 RNA levels and infectious viral load will be evaluated. The proportion of participants with viral load below the level of detection will also be assessed as a measure of antiviral activity. Antiviral activity endpoints are based on EDP-235 acting as an inhibitor of the SARS-CoV-2 3CL protease. Exhibiting slow-onset, slow-reversible binding to the target protein, it is competitive with the peptide substrate and is highly selective for the viral protease over host proteases. In tissue culture models of infection, EDP-235 consistently demonstrated potent antiviral activity against multiple SARS-CoV-2 clinical isolates (EDP-235 Investigator's Brochure). The antiviral activity of EDP-235 supports the development of EDP-235 for treatment of COVID-19. Clinical outcomes, such as time to improvement in targeted signs and symptoms, will be evaluated along with the proportion of participants showing improvement and those participants requiring additional and/or prolonged medical treatment. These endpoints are clinically meaningful measures of the effect of EDP-235 on COVID-19 disease progression.

[redacted]

5.2.3. Rationale for Use of Placebo

This study will use a matched placebo for EDP-235 to allow for unbiased assessment of the clinical safety and efficacy profile of EDP-235. Use of placebo is justified because the approved treatments for COVID-19 (full approval, emergency use authorization, or country-specific equivalent) are for individuals at high risk of disease progression to severe or critical COVID-19.

5.2.4. Rationale for the Participant Population

5.2.4.1. Participants with Mild and Moderate COVID-19

Participants who have mild to moderate symptoms of COVID-19 are treated on an out-patient basis. Therefore, evaluation of this population is reasonable regarding disease progression or improvement.

5.2.4.2. Standard Risk Participants

Participants who are not at high risk for disease progression are included in this study. High risk for disease progression (Appendix 1) is defined based on criteria from the Centers for Disease Control and Prevention 2020.[9] Multiple comorbidities and underlying conditions have been associated with a higher risk for severe COVID-19 (ie, infection resulting in hospitalization, admission to the ICU, intubation or mechanical ventilation, or death).[10] Although high risk participants have an increased risk of developing severe COVID-19 disease, standard risk participants can also develop severe disease and long-term COVID-19 related complications. Of note, in one study, the use of an antiviral agent in standard risk patients with mild or moderate COVID-19 was associated with a non-significant 51% relative risk reduction in hospitalization or death (treatment arm: 5/576; placebo: 10/569), as well as a 62% reduction in COVID-19-related medical visits (eg, emergency room, urgent care, hospital admissions, telehealth calls) per day relative to placebo (p=0.0228).[11]

5.2.4.3. Participants With COVID-19 Signs/Symptoms for ≤5 days

Study participants must have onset of COVID-19 related signs and symptoms within 5 days of randomization. The study aims to evaluate participants early in the clinical course of the disease when COVID-19 is primarily driven by the replication of SARS-CoV-2 and for which the early administration of the study drug is expected to have the greatest impact in lowering viral load and preventing further post-infectious inflammatory response to SARS-CoV-2 infection.

5.3. Justification of EDP-235 Dose

The EDP-235 doses selected for this study are 200 and 400 mg once daily (QD), administered with food, orally for 5 days. These doses were selected based on all relevant available nonclinical and clinical data, including repeat-dose toxicology studies, in vitro pharmacology studies with EDP-235, and clinical safety and PK data from the first-in-human phase 1 study (EDP 235-001). The selected doses are expected to provide exposures in the anticipated therapeutic range.

In Study EDP 235-001, EDP-235 was well tolerated at doses evaluated, including single doses up to [redacted] and multiple doses up to [redacted] once daily for 7 days.

[redacted]

Consistent with the literature for other viral 3CL protease inhibitors, a robust antiviral effect is predicted when unbound plasma concentrations are sustained above multiples of the EC_{90} (ie, concentration at which 90% inhibition of viral replication occurs) for the entire dosing interval. The unbound target minimum plasma concentration (C_{24} or C_{trough}) to be maintained corresponded to the in vitro drug concentration at which 90% inhibition of SARS-CoV-2 viral replication is observed. Available data from nirmatrelvir, a drug with a similar mechanism to EDP-235 (a SARS-CoV-2 3CLpro protease inhibitor, currently under Emergency Use Authorization for subjects infected with SARS-CoV-2 and are at high risk to progression to

severe COVID-19), doses leading to significant reduction in death and hospitalization (~90% reduction compared to placebo), were associated with PK exposures above the in vitro antiviral EC_{90}. [redacted]

The exposures associated with the selected doses are expected to be safe and efficacious.

5.4. End of Study Definition

The end of the study is defined as the date when the last participant completes the last visit, withdraws consent or is lost to follow-up.

The participant is considered completing treatment if the participant completed the treatment period. The participant is considered completing the study if the participant did not permanently discontinue from the study during the duration of the treatment and follow-up periods.

6. STUDY DRUG AND PROHIBITED MEDICATIONS

6.1. Study Drug(s) Administered

Table 2: Study Drug(s) and Study Arms

Study Drugs		
Intervention Label	**EDP-235**	**Placebo to Match EDP-235**
Type	Drug	Drug
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	[redacted]	0 mg
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP/NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	[redacted]	[redacted]

Study Arms			
Arm Title	**EDP-235** [redacted]	**EDP-235** [redacted]	**Placebo**
Arm Type	Experimental	Experimental	Placebo comparator
Dosage	Participants will receive EDP-235 [redacted] QD on Days 1 to 5	Participants will receive EDP-235 [redacted] QD on Days 1 to 5	Participants will receive [redacted] placebo QD on Days 1 to 5

6.2. Administration of Study Drug

Complete instructions for dispensing and administering study drugs are presented in the study specific Pharmacy Manual. Study drug will be dispensed on Day 1. Participants will receive instructions on study drug storage and dosing.

Following randomization on Day 1, participants will receive the first dose of EDP-235 or placebo orally while at the study site. After the first dose, participants will be instructed to take or be administered the study drug orally on each of the 4 subsequent days, at approximately the same time every day (±1 hour). [redacted]

On Day 3 and/or Day 5, if the participant will have the visit at the study site, the visit should be scheduled close to the time the participant normally takes the study drug (± 1 hour) so that it can be taken at the site during the visit. On days participants took their study drug at home, participants should be asked for the time that dose was self-administered and record it in source and the electronic case report form (eCRF).

If a participant forgets to take their study drug at the scheduled time, the dose should be taken as soon as the participant remembers; however, the following rules apply:

- No more than one dose should be taken on any calendar day and
- There must be a minimum of 16 hours between doses.

Site staff will record the time and date of all study drug doses taken at the site.

The investigator or designee will administer the study drug provided for this study exclusively to participants randomized in this protocol. The investigator will not supply study drug to any person not authorized to receive it.

6.3. Preparation, Handling, Storage, and Accountability

Study drug (EDP-235 or placebo) must be dispensed by a licensed pharmacist or other authorized personnel with appropriate training.

[redacted]

Documentation will be maintained at the clinical study site as outlined in the Pharmacy Manual.

Site staff will maintain adequate records of the receipt and disposition of all study drug shipped to and/or procured by the site for this study.

Unused study drug must not be discarded until the end of the study after full drug accountability is performed. Study drug that is dispensed to a participant, but not administered or completely ingested by the participant, must be returned to the pharmacy and the amount remaining recorded in the source documents.

In addition, for drug accountability, participants should bring study drug (including empty bottles) with them to the study site at each visit.

Enanta Pharmaceuticals, Inc. will provide instructions for the return or destruction of any unused study drug in the study specific Pharmacy Manual. If Enanta Pharmaceuticals, Inc. authorizes destruction at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Enanta Pharmaceuticals, Inc., and, that the destruction was adequately documented.

6.4. Assignment to Study Drug

Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign investigational product to each participant.

Eligible participants will be randomized in a 1:1:1 ratio to 5 days of treatment as follows:

- EDP-235 [redacted], orally QD
- EDP-235 [redacted], orally QD
- Placebo, orally QD

Randomization will be stratified by age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days).

6.5. Blinding

6.5.1. Maintaining the Blind

The study will be double-blinded, meaning that the participants, investigators, and site staff will be blinded to treatment assignment until the completion of the study. All study personnel will be blinded to treatment assignment except for the following individuals:

- Unblinded Enanta representatives/unblinded [redacted] statistician not associated with the day-to-day conduct of the study as outlined in a separate DMC charter
- Unblinded members of the DMC for purposes of unblinded data review
- Unblinded Drug Supply Chain personnel for the purpose of monitoring drug supplies
- Unblinded Enanta representatives, [redacted] Medical Safety Services, [redacted], and Regulatory Affairs representatives when required to satisfy regulatory reporting requirements

[redacted]

- Bioanalytical laboratory for the purpose of measuring drug concentrations

During the study, investigators, site personnel, and blinded contract research organization/Sponsor staff will not have access to results for individual participants that could impact clinician assessments, including results for SARS-CoV-2 viral load, respiratory pathogen panel testing, certain biomarkers, and PK.

6.5.2. Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will use the IWRS process which will allow the investigator to have immediate access to the unblinding system.

Unblinding of individual participant treatment by the investigator should be limited to medical emergencies or urgent clinical situations in which knowledge of the participant's study treatment is necessary for clinical management. In situations where the urgency of the case requires immediate action, investigators should use their best judgment, based on the nature and urgency

of the clinical situation, and proceed with unblinding. In emergency situations, the decision to unblind resides solely with the investigator.

Once a participant's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the [redacted] Medical Monitor should be notified within 24 hours of unblinding of the treatment and should inform the Sponsor's Medical Monitor. Information relating to unblinding (eg, the reason, date) should be clearly recorded in the participant's study file.

[redacted] **Medical Monitor 24-Hour Safety Hotline for Protocol Inquiries**	
Europe, Middle East and Africa (EMEA) and Asia-Pacific (APAC)	[redacted]
United States	[redacted]
Latin America	[redacted]

[redacted] Medical Safety Services will unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Enanta Pharmaceuticals, Inc. may unblind individual participants at any time for matters relating to safety concerns.

6.6. Study Drug Compliance

Both accountability and study drug compliance will be reviewed at each study site visit as indicated in the SoA (Section 1.3). The number of capsules will be counted, and the site staff will ask the participants why any doses were missed and document in source, if applicable. Any potential reasons for lack of compliance with dosing will be monitored and followed up by the site staff. Compliance assessment may be completed at the study site or by a study site personnel via a home visit.

For any participant considered to demonstrate continued noncompliance of study drug dosing despite continued educational efforts, the investigator should contact [redacted] the Sponsor's Medical Monitor to discuss possible discontinuation of the participant from the study.

6.7. Dose Modification

Dose modifications are not permitted for participants in this study.

6.8. Continued Access to Study Drug after the End of the Study

There is no continued access to study drug after the end of the study.

6.9. Treatment of Overdose

In this study, an overdose is the receipt of any number of capsules greater than the number of capsules to be taken as outlined in the pharmacy manual.

No specific information is available on the treatment of overdose.

Decisions regarding dose interruptions will be made by the investigator in consultation with the [redacted] Medical Monitor and Sponsor Medical Monitor based on the clinical evaluation of the participant.

6.10. Prohibited Medications

The following treatments will be prohibited from the first dose of study drug on Day 1 through Day 33 or early termination:

- SARS-CoV-2 vaccines
- COVID-19 therapeutics, including all therapies intended for treatment of COVID-19; therapies to manage the symptoms of COVID-19 will be allowed
- Convalescent COVID-19 plasma
- All non-study investigational agents including devices.

[redacted]

7. DISCONTINUATION OF STUDY DRUG AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

In cases of early discontinuation of study drug or early discontinuation/withdrawal from the study, the reason for early discontinuation/withdrawal/lost to follow-up of any participant from the study must be documented in source and on the appropriate eCRF.

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to discontinue study intervention. Reasons for discontinuation include but are not limited to the following:

- AE
- Withdrawal by participant
- Protocol deviation (including noncompliance with study drug or study procedures)
- Pregnancy
- Study terminated by the Sponsor
- Other

If study intervention is discontinued, the participant should, if at all possible, remain in the study and enter the follow-up period. See the Schedule of Assessments (Section 1.3) for data to be collected at the time of discontinuation of study drug and follow-up for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

Participants who discontinue treatment before completing 5 days of dosing will return for an end-of-treatment (EOT) visit immediately (ideally within 24 hours of discontinuing treatment) and will continue with the post-treatment follow-up assessments in the 28-day follow up period. Participants who discontinue the study before Day 33 should return to the study site within 24 hours and no more than 48 hours later to complete the EOFU procedures.

If a participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Enanta Pharmaceuticals, Inc. will retain and continue to use any data collected before such withdrawal of consent.

Randomized participants who withdraw or are withdrawn from the study will not be replaced.

7.3. Lost to Follow-up

Site staff will attempt to contact any participant who does not return to the site for the EOS visit at least three times using the participant's preferred method of communication, followed by a letter requiring delivery notification if the three attempts were unsuccessful. Any participant who still cannot be reached following those attempts will be considered lost to follow-up. These participants will be included in the PK and safety analysis as indicated in Section 11.3.

8. STUDY ASSESSMENTS AND PROCEDURES

Study assessments and their timing are summarized in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Except for Screening and Day 1, assessments may be completed at the study site or via a home visit, if feasible.

8.1. Administrative and Baseline Procedures

8.1.1. Screening Procedures

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm and record eligibility or record reasons for screening failure, as applicable.

Screening procedures will occur after the participant signs and dates an institutional review board (IRB)- or ethics committee (EC)-approved ICF and provides authorization to use protected health information (see Section 12.1.3). After signing the ICF, screening assessments should be performed within 24 hours before randomization. Some procedures performed as part of standard-of-care before Screening may be used in determining study eligibility, such as the SARS-CoV-2 diagnostic test, provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3). Review of laboratory results is not required prior to randomization or dosing.

During the Screening Period, participants will be identified by a unique screening number assigned by the clinical site. Participants who have completed screening assessments and are eligible for participation in the study will be randomized before the first dose of study drug (Day 1) and assigned a unique participant number that will be used to identify the participant throughout the study. The first dose of study drug should be administered on the same calendar day as randomization.

8.1.2. Demographics and Medical, Smoking, COVID-19 Disease History

Demographics and baseline characteristics including age, sex, race (if available), ethnicity (if available), medical history, COVID-19 disease history, and smoking history will be obtained and entered in the respective eCRF as reported at Screening. Significant medical history will be obtained by consulting with the participant. As a general rule, all medical events occurring within the last 6 months should be recorded. For events that occurred more than 6 months ago (and that are not ongoing), only significant or relevant events should be recorded on source and entered in the eCRF. All surgeries occurring in adulthood should be recorded in the eCRF, whereas surgical methods of contraception, if applicable, should only be documented in the source documents.

If there is a question concerning a participant's medical history, medical records may be requested from the participant's primary care physician, as appropriate.

8.1.3. Prior and Concomitant Medications and Therapies

Prior medications and therapies (including diagnostics, surgeries and other interventions) are those that end before the first dose of study drug. Concomitant therapies will include medications and other therapies (including diagnostics, surgeries and other interventions) ongoing at the first dose of study drug or that started any time after the first dose of study drug.

Any medication or therapy taken within 1 month of signing the ICF and during the study will be recorded in source documents and reported on the eCRF with indication, dosage, route of administration, and start and stop dates of administration as applicable. Only relevant medications and therapies should be recorded if they were discontinued more than 1 month before signing the ICF. All prior or concomitant therapeutics/vaccines for COVID-19 including supportive therapies to manage COVID-19 signs/symptoms, must be reported.

All participants will be questioned about concomitant therapies at each study site visit.

8.1.4. Physical Examination

The investigator or designee will perform the physical examination. A full physical examination will be conducted at Screening and will include examination of all pertinent body systems. Any subsequent physical examinations performed at the discretion of the investigator will be targeted to new signs and symptoms including specific assessments of any changes from previous status. Clinically significant abnormalities should be recorded as AEs.

The physical examination performed at Screening will be used as the baseline assessment. If the physical examination was performed on the calendar day before randomization (though within the 24-hour period per protocol), a targeted physical examination may be performed on Day 1 if

deemed necessary by the investigator due to new signs and symptoms or for specific assessments of changes from the previous status.

8.1.5. Height, Weight, and Body Mass Index

Height and body weight should be obtained with the participant in light clothes and no shoes. Height and weight will be documented at Screening only.

Body mass index will be calculated at Screening (to assess eligibility) according to the following equation: BMI = weight (kg)/height $(m)^2$.

8.1.6. Pregnancy and Menopausal Laboratory Testing

All female participants of childbearing potential will undergo a urine pregnancy test at Screening. In addition, on Day 1 and Day 33 (EOT + 4 weeks), a blood sample will be collected for a serum pregnancy test to be performed by the central laboratory. The screening urine pregnancy test results will be used to qualify participants at study entry.

To confirm nonsurgical postmenopausal status for women stating that they are amenorrhoeic for up to 2 years, documentation of follicle-stimulating hormone (FSH) levels >35 mIU/mL will be required. Where such documentation is not available, FSH levels will be measured on Day 1. In such participants, urine and serum pregnancy testing should also be performed at Screening/Day 1, and these participants will be required to follow appropriate contraceptive practices for women of childbearing potential until a confirmatory FSH level is available.

8.1.7. Electronic Device

During Screening, participants will complete the PRO assessment COVID-19 Symptom Diary on an electronic device to assess eligibility.

Randomized participants will complete the PRO assessments COVID-19 Symptom Diary, general impression questions [redacted] on an electronic device. PRO assessments completed after randomization, predose on Day 1 will be the baseline measurement. For the COVID-19 Symptom Diary, if Screening and Day 1 occur on the same calendar day, the Screening Diary entry will be used as the baseline measurement and a separate Day 1 Diary will not be collected.

Participants will receive reminders to complete entries on their own as specified in the SoA. The first entry should be completed after randomization but predose on Day 1. Entries should be completed at approximately the same time every day. Study staff will review the participant's entries online as specified in the SoA. Study staff should contact participants who are not successfully completing Diary and questionnaire entries to retrain or assist participants with any technical issues in completing entries to minimize the amount of missing data.

8.1.8. Other Baseline Procedures

Following randomization on Day 1, participants must complete all baseline assessments before receiving the first dose of EDP-235 or placebo. See the SoA (Section 1.3) for a complete list of baseline assessments.

If Screening and randomization/first dose occur on the same day (Day 1), screening assessments for vital signs and pulse oximetry will be used as baseline values. If Screening (Day -1) and randomization/first dose (Day 1) occur on different calendar days within a 24-hour period, then vital signs and pulse oximetry will be performed again on Day 1 (predose).

8.2. Efficacy Assessments

8.2.1. SARS-CoV-2 Viral Load and Cell Culture Infectivity Assessments

NP swabs for virology assessments, including for SARS-CoV-2 diagnostic test and viral load measurements, will be collected predose at visits specified in the SoA (Section 1.3). Collection, storage, and shipping instructions will be provided in the Laboratory Manual. Multiple NP swab samples may be collected at each timepoint. With the exception of the SARS-CoV-2 diagnostic test that will be performed at the local site laboratory, virology assessments will be analyzed at the central laboratory(ies).

[redacted]

8.2.2. COVID-19 Symptom Diary (Patient Reported Outcome [PRO])

Symptoms of COVID-19 will be reported daily from Days 1 through 33 using the COVID-19 Symptom Diary. on an electronic medium. Participants will self-complete the first COVID-19 Symptom Diary on Day1 before receiving study drug as a baseline measurement. The COVID-19 symptoms and the response options and scoring are shown in Table 3.

Table 3: COVID-19 Symptom Diary

Symptoms	Response Options and Scoring
What was the severity of your [insert symptoms] at its worst over the past 24 hours?	None = 0 Mild = 1 Moderate = 2 Severe = 3
1. Stuffy or runny nose	
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	

Symptoms	Response Options and Scoring
11. How many times did you vomit (throw up) in the last 24 hours?	I did not vomit at all =0 1 to 2 times = 1 3 to 4 times = 2 5 or more times = 3
12. How many times did you have diarrhea (loose or watery stools) in the last 24 hours?	I did not have diarrhea at all = 0 1 to 2 times =1 3 to 4 times = 2 5 or more times = 3
13. Rate your sense of smell in the last 24 hours	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of taste in the last 24 hours	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

8.2.3. COVID-19 Related Medically Attended Visits and Therapies

COVID-19 related medical attended visits include any unscheduled interactions with healthcare professionals other than study staff or designees that are not for routine health maintenance, including virtual visits (telemedicine), telephone calls, hospitalization, in-person emergency room visits, urgent care, or primary care visits, home healthcare visits, or any other in-person visit attended by the participant and a healthcare professional.

Information on admissions to the Intensive Care Unit (ICU) and hospitalizations will be collected, including dates of utilization. Hospitalization is defined as ≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities specifically created to meet hospitalization needs during the COVID-19 pandemic.

COVID-19 related concomitant therapies, including the requirement for supplemental oxygen or invasive or non-invasive mechanical ventilation will be assessed. Increased oxygen supplementation should be assessed by the site and documented in source.

8.3. Safety Assessments

8.3.1. Vital Sign Measurements

Vital signs include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Vital signs will be measured at times shown in the SoA (Section 1.3) after the participant has been supine for a minimum of 5 minutes. Pulse oximetry will be performed to measure oxygen saturation when vital signs are measured.

8.3.2. Electrocardiograms

A resting 12 lead ECG will be performed locally and recorded as specified in the SoA (Section 1.3) after the participant has been supine for 5 minutes and before dosing. A standard bedside 12 lead ECG machine that calculates heart rate and measures PR, QRS, QT, RR, and QTcF intervals will be used.

On Day 1, before dosing, the ECG must be reviewed by the investigator or designee to confirm that no clinically significant cardiac abnormalities are present. The investigator or designee should review the ECG for gross abnormalities and interval measurements of concern (absolute readings). The clinical interpretation by the investigator or designee of the ECGs should be recorded on a hard copy of the ECG (ie, clinically significant or not clinically significant).

An ECG may be repeated at the discretion of the investigator to address suspected errors in performance.

8.3.3. Clinical Safety Laboratory Assessments

Safety laboratory assessments include chemistry, hematology, and coagulation. Blood and urine samples will be collected for analysis of the analytes as shown in Table 1; the SoA (Section 1.3) shows the timing of sample collection. Samples will be processed as indicated in the Laboratory Manual.

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. All laboratory assessments with values considered clinically significantly abnormal during participation should be repeated until the values return to normal or baseline, are no longer considered clinically significant by the investigator or Medical Monitor, or until a pre-defined outcome is reached.

On Day 1, predose blood samples for select clinical laboratory assessments (Table 1) will be performed at the local site laboratory for expedited testing and reporting, and in addition, blood samples will be collected and sent to the central laboratory(ies) for baseline measurements. Subsequent clinical laboratory evaluations will all be performed by the central laboratory(ies). Only central laboratory values will be used for analysis.

8.4. Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in Section 9.1 of this protocol. All AEs and SAEs must be recorded in the source documents and eCRF as described in Section 9.2. At all study site visits, the investigator or designee should inquire about the occurrence of AEs. The following are examples of open-ended questions that may be used to obtain this information: “How are you feeling?”; “Have you had any medical problems recently?”; and “Have you taken any new medicines since your last visit/assessment?” All events of SARS-CoV-2 re-infection should be recorded.

It is the investigator’s responsibility to ensure any necessary additional therapeutic measures and follow-up procedures are performed and documented in the participant source notes and eCRF.

8.5. Pharmacokinetics

Blood (plasma) samples for PK analysis will be collected as outlined in the SoA (Section 1.3). Instructions for the collection and handling of PK samples will be provided in the laboratory manual.

The time and date of PK sample collection should be recorded in source and in the eCRF. In addition, the site should record the date and time of last dose taken before the PK sample collection.

Time windows for intensive PK sampling are shown in Table 4.

Table 4: Time Windows for Intensive PK Sampling*

Intensive Plasma PK Sampling Timepoints	Time Windows
Predose	Within 2 hours before dosing
≤2 hours	± 5 minutes
>2 hours to 8 hours	± 15 minutes

*Only applies to intensive PK subset on Day 1 and 5

[redacted]

8.6. Genetics

Genetics are not evaluated in this study.

[redacted]

[redacted]

[redacted]

9. SAFETY MONITORING AND REPORTING

9.1. Definitions

9.1.1. Pretreatment Events

A pretreatment event is any event that meets the criteria for an AE/SAE and occurs after the participant signs the ICF but before receiving the first administration of study drug.

9.1.2. Adverse Events

An AE is any event, side effect, or untoward medical occurrence in a participant enrolled in a clinical study whether or not it is considered to have a causal relationship to the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory finding outside of normal range with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the investigator, including those requiring therapeutic intervention, physical examination finding, or disease temporally associated with the use of the study drug, whether or not the event is considered related to the study drug.

The occurrence of AEs should be sought by nondirective questioning of the participant at each study site visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between study site visits or through physical examination, laboratory tests, or other assessments.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the participant was enrolled in the study are not to be considered AEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier than planned).

9.1.3. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death: This includes deaths that appear to be completely unrelated to study drug (eg, a car accident)
- Is a life-threatening event: An event that places the participant at immediate 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
- Requires inpatient hospitalization or prolonged hospitalization of an existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication
  - SARS-CoV-2 disease progression
  - Elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the ICF
  - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - Social reasons and respite care in the absence of any deterioration in the participant's general condition
- Results in permanent or prolonged (at least 28 days in duration) disability or incapacity
- Is a congenital anomaly or birth defect in the offspring of a study participant
- Medically important event: An event that may not be immediately life-threatening, or result in death or hospitalization, or require intervention to prevent one of the outcomes listed above but is considered medically significant for other reasons. An opportunistic or otherwise unusual infection for the investigator's practice, such as tuberculosis, will be considered medically significant.

The term severe is used to describe the intensity of a specific event (as in mild, moderate, or severe); the event itself, however, may be of minor medical significance (such as severe headache). This is not the same as serious, which is based on outcome of the event, as described above. Seriousness, not intensity, serves as a guide for defining regulatory reporting obligations.

9.2. Documenting and Reporting of Adverse Events (Including Serious Adverse Events)

Adverse events will be evaluated and documented using the National Institute of Allergy and Infectious Diseases Division of Aids (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1 dated July 2017.

9.2.1. Documenting and Reporting Adverse Events

All AEs reported from the time of informed consent to the EOS visit for each participant will be recorded in the participant's source documents. For participants who did not randomize (ie, screen failures), AEs will only be recorded in the source documents. For participants

randomized into the study, all AEs will be recorded in the participant's AE eCRF and the SAE form (if applicable). The site should record all AEs regardless of the intensity, seriousness, or relationship to study drug.

If a participant discontinues the study prematurely because of an AE, the specific AE should be recorded on the AE eCRF and the participant should be monitored until the event is resolved or deemed stable by the investigator.

Adverse events (serious and nonserious) will be graded in accordance with the DAIDS scale as follows:

- Grade 1 indicates a mild event
- Grade 2 indicates a moderate event
- Grade 3 indicates a severe event
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death

Any recurrence of an AE with similar causality to study drug will be reported as recurrence or exacerbation of the initial event, and not as a new event. Whenever possible, AEs will be reported as a specific diagnosis or syndrome (eg, flu syndrome) rather than as individual signs or symptoms. If no specific diagnosis or syndrome is identified, AEs should be reported as separate and individual events.

An AE includes the following:

- Pre-existing event that increases in frequency or intensity
- Condition detected or diagnosed during the study period, even though it may have been present, in retrospect, before the first dose of study drug
- Laboratory abnormalities outside of normal limits with associated clinical symptoms or suspected latent clinical symptoms in the opinion of the investigator, including those requiring therapeutic intervention

The following events will not be identified as AEs in this study:

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, etc.); however, the condition (the "triggering event") that leads to the procedure may be an AE
- Pre-existing conditions present or detected before the first dose of study drug that do not worsen

9.2.2. Assigning Attribution of Adverse Events

The investigator must attempt to determine the cause of each event. Every effort will be made by the investigator to assess the relationship of each AE to study drug. To ensure consistency of AE/SAE causality assessments, the investigator should apply the following guidelines:

- **Related:** There is an association between the event and the administration of study drug, a plausible mechanism for the event to be related to the study drug and causes other than the study drug have been ruled out, and/or the event reappeared on re-exposure to the study drug.
- **Possibly related:** There is an association between the event and the administration of the study drug and there is a plausible mechanism for the event to be related to study drug, but there may also be alternative etiology, such as characteristics of the participant's clinical status or underlying disease.
- **Unlikely related:** The event is unlikely to be related to the study drug and likely to be related to factors other than study drug.
- **Not related:** The event is related to an etiology other than the study drug (the alternative etiology must be documented in the study participant's medical record).

9.2.3. Classifying Action Taken with Study Drug

In the case of an AE, the actions that can be taken with study drug by the investigator or designee are defined in Table 6.

Table 6: Options for Action Taken with Study Drug

Classification	Definition
Dose not changed	Study drug dose not changed in response to the adverse event.
Drug interrupted	Study drug administration interrupted in response to an adverse event.
Drug withdrawn	Study drug administration permanently discontinued in response to an adverse event.
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" should be used in circumstances when no opportunity to decide whether to continue, interrupt, or withdraw treatment was possible such as when the investigational treatment had been completed before the adverse event began.

9.2.4. Classifying Adverse Event Outcome

For every AE/SAE, the possible outcomes of the event and the definition of the outcome are shown in Table 7. One outcome must be entered into the appropriate field on the AE and (if appropriate) SAE form for each event.

Table 7: Classification and Definition of Adverse Event Outcomes

Classification	Definition
Recovered/resolved	Resolution of an adverse event with no residual signs or symptoms
Recovered/resolved with sequelae	Resolution of an adverse event with residual signs or symptoms
Is Recovering/is resolving	Incomplete improvement to date but adverse event continues to improve/resolve and complete resolution is expected over time
Not Recovered/not resolved	Either incomplete improvement or no improvement of an adverse event, such that it remains ongoing
Fatal	Outcome of an adverse event is death. "Fatal" should be used when death is at least possibly related to the adverse event
Unknown	Outcome of an adverse event is not known (eg, a participant lost to follow-up)

9.2.5. Documenting and Reporting Serious Pretreatment Events and Serious Adverse Events

All SAEs that occur after obtaining informed consent through the EOS visit, regardless of causality, must be reported by the investigator or designee to [redacted] Medical Safety Services and Enanta Pharmaceuticals, Inc. In addition, all SAEs, including those that result in death, that occur after the EOS visit and that are considered related to study drug must be reported to [redacted] Medical Safety Services and Enanta Pharmaceuticals, Inc. within 24 hours of learning of its occurrence. Additional details are provided in the Safety Management Plan. The SAE form should be sent to [redacted] Medical Safety Services.

Serious Adverse Event and Pregnancy Reporting	
[redacted] Medical Safety Services	ICON Safety Fax Lines: • North/South America: [redacted] • Europe/Asia-Pacific: [redacted] [redacted] Drug Safety Centers: • North/South America: [redacted] • Europe/Asia-Pacific: [redacted] Phone: [redacted]

All SAEs will be recorded on the SAE form using a recognized medical term or diagnosis that accurately reflects the event. All SAEs will be assessed by the investigator for severity, relationship to the investigational study drug, and possible etiologies. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing.

For purposes of regulatory safety monitoring, the investigator is required to follow up the event to resolution and report the outcome of the event to [redacted] Medical Safety Services, the [redacted] Project Manager, and Enanta Pharmaceuticals, Inc. using the SAE form.

The investigator or designee is responsible for notifying the Sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE form should be completed for new/initial events as well as to report follow-up information on previously reported events. The investigator or designee is asked to report follow-up information as it becomes available.

Enanta Pharmaceuticals, Inc. or its designee, as study Sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (ie, SUSARs) involving the study drug to all regulatory authorities, and participating investigators, in accordance with United States Food and Drug Administration (FDA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, and/or local regulatory requirements, as applicable.

9.2.6. Documenting and Reporting of Pregnancy

Participants will be counseled to inform the investigator of any pregnancy that occurs during study drug and for 90 days after the last dose of study drug.

If a female participant or the female partner of a male participant becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. The investigator or designee must notify [redacted]Medical Safety Services (Section 9.2.5), the Sponsor's Medical Monitor, and the [redacted] Project Manager within 1 business day of the sites' knowledge of the participant's (or partner's) pregnancy, by utilizing the study-specified pregnancy report form.

If confirmed to be on active drug, the participant or partner will be followed up until the end of the pregnancy and the infant will be followed up for 3 months after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

9.3. Follow-up of Adverse Events and Serious Adverse Events

All AEs (serious and nonserious) will be followed by the investigator until resolution or otherwise explained (see Table 7), the participant dies, the event stabilizes and is not expected to further resolve with the maximum time limit for stabilization defined as 30 days after the occurrence of the event, or when alternative therapy is instituted, whichever occurs first. If alternative therapy is instituted, it should be documented. Enanta Pharmaceuticals, Inc. may request that the investigator perform or arrange for supplemental measurements or evaluations to further clarify the nature of the event. AEs outcomes are determined based on the status at the end of the participant's participation in the study and at the time of database lock.

9.4. Data Monitoring Committee

Safety data from this study will be reviewed by a DMC throughout the study. The DMC will be headed by a DMC Chair and will include one or more physicians with expertise in SARS-CoV-2, consisting of expert(s) independent from the Sponsor. Procedures for data review, including timing and potential outcomes, roles and responsibilities, and interactions with the Sponsor [redacted] will be governed by a separate DMC charter.

10. STUDY DISCONTINUATION RULES

10.1. Study Stopping Rules

If any of the following events occur, enrollment will be paused pending a full review of all available clinical safety data and discussion with the DMC:

- >1 subject experiences a similar Grade 4 study drug-related or possibly related AE
- >1 subject experiences a similar study drug-related or possibly related SAE

Unless the participant's randomization code is unblinded by the Sponsor for clinical reasons, only the DMC will have access to unblinded data.

If >2 subjects experience a similar Grade 3 (severe) clinical or laboratory AE related or possibly related to the study drug, a full review of all available AE and relevant laboratory data will take place with the DMC within 15 days.

The study will be terminated or amended to terminate the treatment arm associated with the AE of concern if it is deemed, following discussion with the DMC, that the study drug and not COVID-19 or another factor was most likely to be accountable.

10.2. Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Incidence or severity of AEs in this study indicates a potential health hazard to participants
- Participant enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study
- Decision from the IRB/EC or regulatory authority to terminate the study

If the study is suspended or terminated for safety reasons, Enanta Pharmaceuticals, Inc. will promptly notify the investigators and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. The investigator is responsible for promptly informing the IRB/EC and providing the reasons for the suspension or termination of the study.

10.3. Site Termination

A single site may warrant termination under the following conditions:

- Failure of the site to enroll participants into the study at an acceptable rate
- Failure of the site to comply with pertinent governmental regulations as appropriate
- Submission of knowingly false information from the research facility to the Sponsor, Clinical Monitor, or governmental authority
- Failure to adhere to the protocol requirements
- Data recording is inaccurate or incomplete
- Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study

10.4. Study Termination Procedures

If the study is terminated by Enanta Pharmaceuticals, Inc. for one of the reasons listed previously, or upon completion of the study, the following activities must be conducted by the Study Monitor and/or site staff:

- Return of all study data to Enanta Pharmaceuticals, Inc. or designee
- Respond to and complete all requests for data clarifications
- Accountability and final disposition of used and unused study drug
- Review of site records for completeness
- Shipment of all applicable biological samples (including PK samples) to the designated laboratory

11. STATISTICAL CONSIDERATIONS

11.1. General Considerations

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in an Analysis Plan. The Statistical Analysis Plan (SAP) of this study will be dated and maintained by the Sponsor Enanta Pharmaceuticals, Inc. or its designee. This documentation may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Continuous endpoints will be summarized using n, mean, standard deviation, median, 25^{th} quartile, 75^{th} quartile, minimum, and maximum values. Categorical endpoints will be summarized by the number of participants meeting the endpoint and the percentage of participants out of the appropriate population. The denominator will be displayed when needed. Statistical inference will be performed as appropriate. Inferential testing will be conducted using a two-sided alpha of 0.05, unless stated otherwise. Stratification factors will include age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days)

at Screening. Time to event variables will be analyzed using the Kaplan-Meier method. This method will be applied to derive the median event time and a confidence interval (CI) for the median for each treatment arm.

Imputation of missing data within efficacy variables and endpoints will be computed according to the rules specified in the SAP.

Any change to the data analysis methods described in the protocol will require an amendment if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report or SAP. The SAP will be developed and finalized before database lock. Changes to the SAP may not be made after unblinding of treatment assignments (after database lock).

11.2. Sample Size Considerations

Approximately 200 participants are planned. This sample size was selected to provide adequate safety data and evaluation of antiviral activity, PK, and clinical efficacy endpoints.

11.3. Analysis Populations

The following analysis populations are planned:

- *Randomized Population:* All participants who are randomized.
- *Safety (SAF) Population:* All participants in the Randomized Population who receive at least one dose of study drug. Participants will be analyzed in the treatment group that corresponds to the study drug received during the study.
- *Intent-to-Treat (ITT-c) Population:* All participants in the Safety Population with their positive SARS-CoV-2 status confirmed by central RT-PCR viral load at baseline >LLOQ and with at least one post-baseline primary efficacy measurement. Participants will be analyzed as randomized. The ITT-c Population is designated as the primary efficacy population.
- *Per Protocol (PP) Population:* All participants in the ITT-c Population who receive all planned doses of study drug and do not have major protocol deviations that may unduly influence efficacy outcome. Participants will be analyzed in the treatment group that corresponds to the study drug received during the study.
- *PK Population:* All participants in the Safety Population receiving active study drug and having measurable plasma concentration of study drug at any timepoint.

11.4. Participant Disposition and Demographic Data

The number of participants screened, randomized, and in the SAF, ITT-c, PP, and PK populations will be summarized using frequencies and percentages. The denominator for the calculation of percentages will be from the number of participants randomized.

The following categories will also be summarized for participant disposition:

- Completed study drug per the protocol

- Discontinued study drug early and the reason for discontinuation
- Completed the study
- Discontinued from the study early and the reason for discontinuation

Participant demographics will be summarized by treatment group for all participants in the SAF, modified ITT and PP Population. Appropriate baseline characteristics will be included in addition to demographic characteristics. No statistical testing will be performed.

11.5. Safety Analyses

Safety analyses will be based on the Safety Population, Statistical methods for the safety analyses will be descriptive in nature. Safety data, including AEs, SAEs, vital sign measurements, concomitant medications, and laboratory values, will be summarized separately by treatment group. Change from Baseline will be included in summary tables for vital sign measurements and laboratory parameters. Shift tables will also be generated by laboratory analyte. All laboratory data will be included in the data listings, and all test values outside the normal range will be flagged.

Analysis for the primary objective will be conducted after all randomized subjects complete the EOFU visit.

11.5.1. Adverse Events

Adverse events will be summarized by the Medical Dictionary for Regulatory Activities system organ class and preferred term by treatment group. All participants in the SAF Population will be included in the summaries. Treatment emergent AEs (TEAEs) are defined as reported AEs that first occurred or worsened during the post-Baseline phase compared with Baseline. The maximum severity at Baseline will be used as baseline severity. If the maximum severity during post Baseline is greater than the maximum baseline severity, then the event is considered treatment emergent. No statistical testing will be performed.

Summaries of AEs will include the following at a minimum:

- An overall summary of AEs with a line for each of the categories provided below:
    - TEAEs
    - Related TEAEs
    - Maximum severity TEAE
    - TEAEs by severity
    - TEAEs leading to study drug discontinuation
    - AEs leading to death
    - SAEs
    - Related treatment emergent SAEs

11.5.2. Clinical Laboratory Data

Laboratory assessments will be reported as mean change from Baseline across scheduled visits, and as the incidence rate of shift change from Baseline. Shift from Baseline tables will be generated for each treatment group for selected analytes. Laboratory shifts will be displayed as treatment-emergent abnormal, high, or low results. The following details the summary types where LLN = lower limit of normal and ULN = upper limit of normal.

For categorical tests: Treatment emergent abnormal is defined as a change from normal at Baseline to abnormal at any post-Baseline visit.

For continuous tests:

- Treatment-emergent high is defined as a change from a result less than or equal to the high limit at Baseline to a value greater than the high limit at any time post-Baseline.

  Results will be reported according to any value greater than the high limit, any value greater than 2× ULN and 3× ULN.

- Treatment-emergent low is defined as a change from a result greater than or equal to the low limit at Baseline to a value less than the low limit at any time post-Baseline.

  Results will be reported to any value less than the lower limit, any value less than 2× LLN and 3× LLN.

11.5.3. Vital Sign Measurements

The incidence rate of participants with treatment-emergent vital sign changes at any post-Baseline visit will be summarized. Specific criteria for the classification of treatment emergent will be documented in the SAP. Vital sign observed, change, and percentage change will be summarized by treatment over visits. Pulse oximetry measurements will be summarized by visit and treatment.

11.5.4. Electrocardiograms

ECG data will be provided in data listings.

11.5.5. Concomitant Medications and Therapies

The number and percentage of participants taking concomitant medications will be coded according to the latest World Health Organization Anatomical Therapeutic Chemical (ATC) Classification and World Health Organization preferred term. Concomitant therapies will be coded according to Medical Dictionary for Regulatory Authorities (MedDRA). Participants in the SAF Population will be summarized by treatment group.

11.6. Efficacy and Antiviral Activity Analyses

An analysis of covariance (ANCOVA) model, with treatment group, serostatus (i.e., seropositive or seronegative) stratification factors, ie, age (≤50 years or 51 to 64 years) and duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days as factors, and baseline score as the covariate, will be used for treatment comparisons.

The least-squares means and two-sided 95% confidence intervals will be presented for individual groups and the difference between groups.

Categorical variables will be summarized and the between group comparison will be analyzed using a Cochran-Mantel-Haenszel test controlling for the stratification factors and serostatus.

The Kaplan-Meier method will be applied to time to event variables to derive the median event time and a CI for the median for each treatment arm. Descriptive statistics on the Kaplan-Meier curve will at least include the median and 95% CI. In addition, the between group comparison will be conducted using the Cox proportional hazard model adjusted for stratification factors, serostatus, and the associated baseline values. The proportion of participants with the events will also be summarized.

11.6.1. Multiplicity Testing Procedure

There is no planned multiplicity control for the analysis of efficacy endpoints.

11.6.2. Handling of Missing Data

For missing efficacy data other than time to event endpoints, the last observation carried forward approach will be used where appropriate. For the time to event endpoints, the censoring will occur at the end of the study.

11.7. Pharmacokinetic Analyses

Summary of plasma PK concentration data will be descriptive in nature. Mean plasma concentration time figures may be created for EDP-235, as allowed by the data. Additional details will be provided in the SAP.

11.8. Subgroup and Covariate Analyses

Subgroup analyses will be performed on the primary endpoint using ITT-c Population.

Subgroup analyses for the primary efficacy endpoint may be considered for the following baseline variables, if there are enough participants in the subgroups to support the planned analyses:

- Sex (female vs male);
- Age (<50 years of age vs 51 to 64 years of age);
- Region;
- Duration of COVID-19 symptoms (≤3 days or >3 days and ≤5 days),
- Serostatus (ie, seropositive or seronegative)

The subgroup analysis will be based on an ANCOVA model with treatment group, serostatus, stratification factor, subgroup, and subgroup by treatment interaction as factors, and baseline value as a covariate.

[redacted]

12. STUDY ADMINISTRATION

12.1. Ethical Considerations

12.1.1. Ethical Conduct of the Study

The study will be conducted in compliance with this protocol, principles of E6 Good Clinical Practice: Consolidated Guidance (ICH-GCP), Declaration of Helsinki, and all applicable local laws and regulations governing clinical studies.

12.1.2. Ethical Review

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by an appropriate IRB/EC that conforms to the regulations set forth in FDA 21 Code of Federal Regulations (CFR) Part 56 and other national, country, and regional regulations as applicable. The investigator must also submit the ICF, any other written documentation provided to the participant, and all advertisements that may be used for study-specific recruitment to the IRB/EC for review and approval before commencing study specific assessments. If it is necessary to amend the protocol during the study, then it is the responsibility of the investigator to ensure that IRB/EC approval is obtained before implementation of the amended procedures. It is also the responsibility of the investigator to provide the IRB/EC with any SAE or Investigational New Drug safety reports. A copy of the ICF approved by the IRB/EC must be forwarded to Enanta Pharmaceuticals, Inc. for regulatory purposes.

12.1.3. Written Informed Consent

The investigator or designee must explain to each participant the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in 21 CFR Part 50, and other applicable national and local regulations governing informed consent.

Each participant must provide a signed and dated ICF before enrollment into this study. Signed consent forms must remain in each participant's study file and be available for verification by study monitors at any time. In accordance with individual local and national participant privacy regulations, the investigator or designee must explain to each participant before Screening that for the evaluation of study results, the participant's protected health information obtained during the study may be shared with Enanta Pharmaceuticals, Inc. and its designee, regulatory agencies, and IRBs/ECs. As the study Sponsor, Enanta Pharmaceuticals, Inc. will not use the participant's

protected health information or disclose it to a third party without applicable participant authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each participant, or if appropriate, the participant's legal guardian. If a participant or participant's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the participant or participant's legal guardian and to ensure that no further data will be collected from the participant. Any data collected on the participant before withdrawal will be used in the analysis of study results.

12.1.4. Investigator Compliance

The investigator/institution should conduct the study in compliance with the protocol agreed to by the Sponsor and regulatory authorities and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the Sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to study participants, or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number). The investigator should document and explain any deviation from the approved protocol.

12.2. Data Collection

Study data will be entered into an eCRF by site staff. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the participant's eCRF. Participants who did not randomize will not be entered into the clinical database. See Section 4.3 for additional details regarding screen failure data collection. Reasons for screen failure will be collected in the interactive response technology (IRT) system. In addition, criteria for confirming eligibility will be collected in IRT. Source documentation supporting the clinical data should indicate the participant's participation in the study and should document the dates and details of study procedures, AEs, other observations, and participant status. The investigator or designated representative should complete the eCRF as soon as possible after information is collected. An explanation should be provided for all missing data as required per CRF.

Assessments that occur due to standard of care are not required to be collected as unscheduled data in the eCRF. In addition, it is recommended unscheduled assessments be entered if associated with an AE during study conduct before the participant completes the EOS Visit. The participant completion date of the study is associated with the last required assessment conducted for the EOS Visit.

After the participant has completed the study, the investigator must review and sign the signature page of the eCRF indicating that he or she has reviewed the completed eCRF and pertinent clinical data for that participant and that, to the best of his or her knowledge, all data recorded in the eCRF accurately reflects the participant's clinical performance in the study.

12.3. Study Monitoring

Representatives of Enanta Pharmaceuticals, Inc., [redacted], or other designees will monitor this study until completion. Monitoring will be conducted through both on-site and remote visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. The Study Monitor will ensure that the investigation is conducted according to protocol and regulatory requirements, and as described in the Study Monitoring Plan.

Every effort will be made to maintain the anonymity and confidentiality of all participants during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/EC, representatives of Enanta Pharmaceuticals, Inc., its designated agent, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or study site records of all participants enrolled in this study. A statement to this effect will be included in the ICF authorizing the use of protected health information.

12.4. Quality Assurance

At its discretion, Enanta Pharmaceuticals, Inc. or its designees may conduct a quality assurance audit of this study. If such an audit occurs, the investigator will give the auditor direct access to all relevant documents and will allocate his or her time and the time of his or her site staff to the auditor as required. In addition, regulatory agencies may conduct an inspection of this study. If such an inspection occurs, the investigator will notify the Sponsor and [redacted] will allow the inspector direct access to all source documents, eCRFs, and other study documentation for source data check and/or on-site audit inspection.

12.5. Retention of Records

The site will retain a copy of all study records in a safe, secure, and accessible location for a minimum of 2 years after notification by Enanta Pharmaceuticals, Inc. that the investigations of EDP-235 have been discontinued or for 2 years following marketing approval of the drug, after which time, Enanta Pharmaceuticals, Inc. will be contacted for instructions on the disposition of study materials. Study records will contain all of the appropriate documents as detailed in Section 8.0 of the ICH-GCP E6.

12.6. Information Disclosure

12.6.1. Confidentiality

Participant names or any other identifiers will remain confidential and will not be supplied to Enanta Pharmaceuticals, Inc. or its designees. Only participant number and year of birth with age will be recorded on the eCRF. If the participant name appears on any other document collected (eg, unit discharge summary), it must be redacted before the document is transmitted to Enanta Pharmaceuticals, Inc. or its designees. All study findings will be stored in electronic databases. As indicated in the ICF, participants will give permission for representatives of the Sponsor, regulatory authorities, and the IRB/EC to inspect their medical records to verify the information collected. Participants will be informed that all personal information made available for

inspection will be handled in the strictest confidence and in accordance with local data protection/privacy laws.

Individual participant medical information obtained during this study is confidential and its disclosure to third parties other than those mentioned in the preceding paragraph is prohibited. Medical information obtained during this study may be provided to the participant's personal physician or other appropriate medical personnel when required in connection with the participant's continued health and welfare and with the participant's prior knowledge and permission.

12.6.2. Publication Policy

It is the intention of Enanta Pharmaceuticals, Inc. to publish the results of this study in their entirety within a reasonable period of time following conclusion of the study. The Sponsor will determine when and where data will be first disclosed.

All information generated from this study is the proprietary property of Enanta Pharmaceuticals, Inc. The Sponsor, Enanta Pharmaceuticals, Inc. reserves the right, among other things, to the following:

- Modify or amend study material to ensure that no confidential or proprietary information is disclosed
- Ensure that the reported data are factually correct
- Utilize the information generated from or as a result of this study in any manner it deems appropriate, including but not limited to regulatory submissions, annual reports, and other scientific or business affairs of the company
- Modify the publication or disclosure or delay it a sufficient time to allow Enanta Pharmaceuticals, Inc.to seek patent protection of any invention contained therein.

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[redacted]

APPENDIX

APPENDIX 1. CONDITIONS ASSOCIATED WITH HIGH RISK FOR SEVERE COVID-19

Asthma

Bronchiectasis

Cancer

Cerebrovascular disease

Chronic kidney disease

Chronic liver disease (cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis)

COPD

Cystic fibrosis

Diabetes mellitus, type 1

Diabetes mellitus, type 2

Gestational diabetes

Disabilities, including Down Syndrome

HIV

Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)

Interstitial lung disease

Mental health conditions (such as mood disorders, including depression, and schizophrenia spectrum disorders)

Neurologic conditions (Dementia)

Obesity (BMI ≥30 kg/m^2)

Physical inactivity

Pregnancy and recent pregnancy

Primary immunodeficiencies

Pulmonary hypertension and pulmonary embolism

Smoking, current and former

Solid organ or blood stem cell transplantation

Tuberculosis

Use of corticosteroids or other immunosuppressive medications

Source: https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/underlying-evidence-table.html
Accessed 25 September 2022