A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Bemnifosbuvir in High-Risk Outpatients with COVID-19

Sponsor Protocol Number:	AT-03A-017
EU CT Number:	2023-504540-33-00
Investigational Product(s):	Bemnifosbuvir Hemisulfate (BEM; AT-527)
Sponsor:	Atea Pharmaceuticals, Inc. 225 Franklin Street Suite 2100 Boston, MA 02110 USA +1 (857) 284-8891

COMPLIANCE

The study will be conducted in accordance with this protocol, the ethical principles in the latest version of the Declaration of Helsinki, and standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.

Protocol Version		**Date**
2.0	**FINAL**	**15Jun2023**
1.0	**FINAL**	**08Sept2022**

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SYNOPSIS

Protocol Title:	A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Bemnifosbuvir in High-Risk Outpatients with COVID-19
Protocol Number:	AT-03A-017
Clinical Phase:	3
Primary Objective:	To evaluate the efficacy of bemnifosbuvir (BEM) compared with placebo in reducing all-cause hospitalization or all-cause death in COVID-19 outpatients receiving only supportive care.
Secondary Objectives:	To evaluate the efficacy of BEM compared with placebo on: • COVID-19 related hospitalization or all-cause death through Day 29 • All-cause death through Day 29 and Day 60 • COVID-19-related complications (eg, death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, cardiac failure) through Day 29 • COVID-19-related medically attended visits (hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit) or all-cause death through Day 29 and Day 60 • COVID-19 symptom relapse To evaluate the antiviral activity of BEM compared with placebo on viral load rebound To evaluate the safety of BEM compared with placebo
Exploratory Objectives:	To evaluate the efficacy of BEM compared with placebo on: • Alleviation or improvement of individual COVID-19 symptoms • Return to usual (pre-COVID-19) health • Requirement for post-randomization rescue therapy • The antiviral activity of BEM compared with placebo To assess plasma concentrations of AT-511 (free base form of AT-527 [BEM]) and its metabolites
Study Design:	• Randomized, double-blind, placebo-controlled study • BEM or matching placebo will be administered twice daily (BID) for 5 days (10 doses)

	• Locally available standard of care (SOC) treatment should be initiated in parallel in addition to study drug (add-on). SOC treatments with direct antiviral activity against SARS-CoV-2 are allowed but should be initiated during screening and/or within 24 hours prior to or after randomization. • Subjects will be randomized 1:1 (active:placebo) to one of the following arms: – 550 mg BEM (2 x 275-mg tablets) BID for 5 days – Placebo (2 tablets) BID for 5 days *Note: Each dose consists of 2 tablets. On each dosing day, 2 tablets will be taken for the morning dose and 2 tablets will be taken for the evening dose. The total treatment course consists of 10 doses over 5 days (20 tablets total).* • Randomization will be stratified by geographic region (North America, Europe, Asia, and rest of world [ROW]), age (< 65 years old vs ≥ 65 years old) and by the type of SOC which the investigator plans to administer in parallel at time of study drug initiation. The type of SOC received will be used to classify subjects into two categories: a. Combination antiviral stratum (subsequently referred to as the combination antiviral population): In addition to study drug, the subject will be initiated on a local SOC regimen which includes a treatment with direct SARS-CoV-2 antiviral activity. Examples include nirmatrelvir/ritonavir, molnupiravir, favipiravir, monoclonal antibodies (mAbs). b. Supportive-care-only stratum (subsequently referred to as the supportive-care-only population): the SOC regimen the subject will receive does not include any treatment with direct SARS-CoV-2 antiviral activity. *Note: Although randomization is stratified by whether COVID-19 drugs with antiviral effects are administered, both strata allow local SOC therapies without direct antiviral effects (ie, corticosteroids).* *Note: Patients who require SOC treatment with a non-compatible antiviral treatment, defined as those with a potential drug-drug interaction (DDI) with BEM (eg, remdesivir), are excluded.* *Note: As ritonavir is a major P-gp inhibitor, subjects enrolled in the combination antiviral group who are taking nirmatrelvir/ritonavir should not take nirmatrelvir/ritonavir until at least 2 hours after taking study drug* Study Population • High-risk outpatients with mild or moderate COVID-19 – Age and comorbidities will determine risk and eligibility (see inclusion criteria)

	• Onset of COVID-19 symptoms will have occurred ≤ 5 days before randomization
Duration of Study:	• The primary study period is up to 30 days, including up to 1 day for screening and 29 days from randomization • Extended follow-up data will be collected through Day 60 for mortality and medically attended visit assessment. The Day 60 follow-up contact marks the end of study participation for each subject and the study ends when the last subject completes the Day 60 follow-up contact.
Number of Subjects:	• Approximately 2510 eligible subjects with COVID-19 will be enrolled – 2210 subjects are expected to comprise the supportive-care-only population – Up to 300 subjects are expected to comprise the combination antiviral population
Inclusion Criteria:	1. Willing and able to provide informed consent. 2. Positive SARS-CoV-2 diagnostic test (reverse transcription polymerase chain reaction [RT-PCR] or validated rapid antigen test) conducted ≤ 5 days prior to randomization. *Note: The test may be obtained locally. A documented historical record of positive result (RT-PCR or validated rapid antigen test) from a test conducted ≤ 5 days prior to randomization is acceptable.* 3. Mild or moderate COVID-19 with symptom onset ≤ 5 days before randomization and at least one COVID-19 related symptom present at time of screening: • Mild COVID-19: – Symptoms of mild illness with COVID-19, which could include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste or smell, without shortness of breath or dyspnea – No clinical signs indicative of moderate, severe, or critical illness severity • Moderate COVID-19: – Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion – Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, heart rate

	≥ 90 beats per minute; with saturation of oxygen (SpO_2) > 93% on room air – No clinical signs indicative of severe or critical illness severity 4. For females of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 30 days after the final dose of study drug. 5. Females of childbearing potential must have a negative pregnancy test prior to initiation of study drug. 6. Subject must be able to take oral tablet medications. 7. Subject is, in the opinion of the investigator, willing and able to comply with the study drug regimen and all other study requirements. 8. Subject must be high risk, defined below. • Age ≥70 years OR • Age ≥55 years with one of the following risk factors: – Obesity (body mass index [BMI] ≥30 kg/m^2) – Diabetes mellitus – Cardiovascular disease (including congenital heart disease) or hypertension (with at least one medication recommended or prescribed) – Chronic lung disease requiring routine therapy (eg, chronic obstructive pulmonary disease [COPD], moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) OR • Age 50 to 54 inclusive with two of the following risk factors: – Obesity (body mass index [BMI] ≥30 kg/m^2) – Diabetes mellitus – Cardiovascular disease (including congenital heart disease) or hypertension (with at least one medication recommended or prescribed) – Chronic lung disease requiring routine therapy (eg, chronic obstructive pulmonary disease [COPD], moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension) OR

	• Age ≥18 years with one of the following: – Down syndrome – Sickle cell disease – Dementia – Parkinson's disease – Care home residents – One of the following immunocompromising conditions or immunosuppressive treatments: o On immunosuppressive regimens including chemotherapy, for the treatment of cancer o Hematologic malignancy associated with poor response to COVID-19 vaccines (eg, CLL, non-Hodgkin lymphoma, multiple myeloma, acute leukemia) o Being within 2 years of a hematopoietic stem cell transplant o Receipt of a solid-organ transplant and on immunosuppressive therapy o Human immunodeficiency virus (HIV) infection (untreated) or with $CD4^+$ T lymphocyte count <350 cells per cubic millimeter (mm^3) o Moderate or severe primary immunodeficiency o Active treatment with an immunosuppressive medication regimen (eg, high-dose corticosteroids [ie, 20 mg of prednisone daily or equivalent for ≥2 weeks], alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents that are severely immunosuppressive, tumor necrosis factor [TNF] blockers, biologics that are immunosuppressive) • Enrollment of 24 high-risk adolescents (≥ 12 years to 17 years) will be allowed after the planned, pre-specified interim analysis for which 65% of the supportive-care-only strata completed the follow-up period (Day 29). A DSMB recommendation that the study continue at this interim analysis point will trigger enrollment of adolescents. The Sponsor will notify sites when enrollment of adolescent subjects is permitted. *Note: "High-risk" subjects in this age group are identical to high-risk subjects ≥ 18 years.*
Exclusion Criteria:	1. Female subject is pregnant or breastfeeding.

	2. Clinical signs or symptoms indicative of severe or critical COVID-19 illness, including any of the following: shortness of breath at rest, respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, $SpO_2 \leq 93\%$ on room air, partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) <300, shock (defined by systolic blood pressure <90 mm Hg or diastolic blood pressure < 60 mm Hg or requiring vasopressors), multi-organ dysfunction/failure, respiratory distress, respiratory failure; requirement of endotracheal intubation, mechanical ventilation, oxygen delivered by high-flow nasal cannula, noninvasive positive pressure ventilation, extracorporeal membrane oxygenation (ECMO). *Note: Subjects receiving chronic supplemental oxygen by nasal cannula are eligible for the study if there has been no increase in baseline oxygen requirement/settings.* 3. Admitted to a hospital within 90 days prior to randomization due to COVID-19 or is hospitalized (inpatient) for any reason at randomization. *Note: If local policy requires COVID-19 isolation or internment in a hospital or similar facility, but subjects otherwise meet inclusion criteria, this exclusion may not apply. However, subjects under clinical observation at a clinic/study site or hospital with plans to remain in that setting overnight are not study eligible.* 4. In the opinion of the investigator, is likely to experience imminent deterioration and require hospitalization within 24 hours. 5. Use of other investigational drugs within 30 days prior to planned dosing, or plans to enroll in another clinical trial of an investigational agent while participating in the present study, except for unblinded protocols that don't include direct acting antivirals for COVID-19 (eg, open-label oncological regimen variations or biologic studies). *Note: Prior to enrolling subjects that are on other open-label studies, it is the site's responsibility to ensure that the study criteria for that study allow for enrollment into this study.* 6. Initiation or planned initiation of remdesivir for treatment of the current SARS-CoV-2 infection. 7. Requirement of any prohibited medications, as described in Section 5.7, including either hydroxychloroquine or amiodarone within 3 months prior to screening. (see rationale in Section 5.7.5) *Note: Subjects who had already initiated any COVID-19 drug with antiviral effects intended to treat symptomatic SARS-CoV-2 infection (≥24 hours prior to randomization) will be excluded. During screening (or within 24 hours prior to or after randomization), locally available COVID-19 drugs with antiviral effects (including but not limited to nirmatrelvir/ritonavir, molnupiravir, favipiravir, mAbs) will be permitted.*

	8. Other known active viral or bacterial infection at the time of screening, such as influenza (ie, as verified by a locally available rapid flu test at screening) and respiratory syncytial virus (RSV). *Note: This exclusion does not apply to subjects with stable chronic viral infections, such as chronic hepatitis C virus (HCV) or HIV providing other eligibility criteria are met*. 9. Receiving dialysis or have known severe renal impairment (ie estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula). Note: If the investigator suspects the subject may have eGFR <30 mL/min/1.73 m^2, a confirmatory test should be performed at screening to confirm eligibility before the first dose of study drug. 10. History of severe hepatic impairment (Child-Pugh Class C) 11. Known allergy or hypersensitivity to components of study drug. 12. Malabsorption syndrome or other condition that would interfere with enteral absorption. 13. Any clinically significant medical condition or known laboratory abnormality that, in the opinion of the investigator, could jeopardize the safety of the subject or impact subject compliance or safety/efficacy observations in the study.
Test Product:	• BEM will be provided as 275 mg tablets (designated as formulation A2-275 mg) • Matching BEM-placebo tablets will also be provided.
Dose and Mode of Administration:	• BEM and placebo to be administered orally • Doses and frequency as described in the protocol
Data Safety Monitoring Board (DSMB)	• An independent DSMB will evaluate safety, efficacy, and futility, as described in the DSMB charter
Study Endpoints	The primary efficacy endpoint is the proportion of subjects in the supportive-care-only population who are hospitalized for any cause or died due to any cause through Day 29. Secondary endpoints are: <u>Efficacy:</u> • Proportion of subjects with COVID-19-related hospitalization or who died due to any cause through Day 29

	• Proportion of subjects who died due to any cause through Day 29 and Day 60 • Proportion of subjects with COVID-19-related complications (eg, death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, cardiac failure) through Day 29 • Proportion of subjects with COVID-19-related medically attended visits (hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit) or who died due to any cause through Day 29 and Day 60 • Proportion of subjects with COVID-19 symptom relapse through Day 29 • Proportion of subjects with viral load rebound (term to be defined in the Statistical Analysis Plan [SAP]) through Day 29 <u>Safety:</u> • The incidence and severity of adverse events (AEs) and serious adverse events (SAEs) Exploratory endpoints are: <u>Efficacy:</u> • Time to alleviation or improvement of individual COVID-19 symptoms • Time to self-reported return to usual (pre-COVID-19) health • Proportion of subjects requiring post-randomization rescue therapy *Note: For subjects randomized into the combination antiviral population, antiviral medications administered post-baseline within 24 hours of first study drug, as part of the combination regimen, are not considered rescue medication.* *Note: Rescue therapy for the purpose of the endpoint includes only treatments with direct activity against SARS-CoV-2; and that is administered for COVID-19-related clinical decline.* • Duration and severity of COVID-19 symptom relapse • Proportion of subjects with both COVID-19 symptom relapse and viral load rebound • Change from baseline in amount of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral RNA as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) over time

	• Time to cessation of SARS-CoV-2 viral shedding by RT-qPCR • Proportion of subjects negative for SARS-CoV-2 viral RNA by RT-qPCR over time • Area under the curve (AUC) in the amount of SARS-CoV-2 viral RNA as measured by RT-qPCR • Proportion of subjects with treatment-emergent mutations in SARS-CoV-2 viral genes • CCI [redacted] Pharmacokinetics: • Plasma concentrations of AT-511 (free base form of AT-527 [BEM]) and its metabolites The primary efficacy endpoint will also be assessed in the combination antiviral population as a secondary endpoint. All secondary CCI [redacted] endpoints will be assessed in both the supportive-care-only population, and the combination antiviral population
Statistical Methods:	The primary efficacy analysis will be conducted using the modified intent-to-treat-S (mITT-S) population, which is defined as all randomized subjects who received ≥ 1 dose of study drug, have ≥ 1 positive SARS-CoV-2 result through Day 5 (from nasopharyngeal [NP] swab samples), and who are stratified into the supportive-care-only population. The primary efficacy objective of this study is to evaluate the efficacy of BEM based on the proportion of patients who are hospitalized for any cause or who died due to any cause through Day 29 in the supportive-care-only population. This proportion of patients will be compared between the BEM and placebo arms using a Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factors of age and region. The CMH p-value and estimated common risk difference, odds ratio and relative risk, along with the corresponding 95% confidence intervals (CIs) for these estimates, will be presented. The primary estimand will be the difference in the proportion of all-cause hospitalization and all-cause mortality between BEM-treated and placebo-treated subjects, regardless of adherence to study drug and subsequent interventions, in non-hospitalized COVID-19 patients whose initial course of treatment was supportive care only. Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. For the intercurrent events of rescue (eg intervention with remdesivir) and concomitant COVID-19 medications, a treatment policy approach will be taken, whereby use of rescue and concomitant medications will be ignored, and observations collected after they are administered to the patient will be used. In addition, patients will be followed, assessed, and analyzed irrespective of their

	completion of the course of the study treatment. The analysis will be performed based on observed data, and the following measures will be used to reduce missing hospitalization/death data: electronic Case Report Forms (eCRFs) capturing clinical information that may be indicative of hospitalization will be reviewed to mitigate the risk of unreported hospitalizations, and study staff may use a public information source to obtain information about survival status if a patient withdraws from the study. The primary efficacy endpoint will also be assessed in the combination antiviral population as a secondary endpoint. Other secondary efficacy endpoints will be analyzed using methods similar to those specified for the primary efficacy endpoint. Data handling, analysis populations, and specification of statistical testing for secondary efficacy endpoints, with methods used to control overall type I error, will be detailed in the SAP. Statistical analyses of exploratory efficacy endpoints, and any exploratory subgroup analyses will be detailed in the SAP An interim futility analysis and an interim efficacy/futility analysis are planned after 30% and 65% of subjects in the supportive-care-only population respectively are enrolled and have completed the follow-up period (Day 29). Testing will employ alpha spending and non-binding beta spending, both according to Lan-Demets approximation of O'Brien Fleming method. The study is powered to detect a true 60% reduction in the hospitalization and all-cause mortality rate with BEM as compared to placebo. With 2100 evaluable supportive-care-only subjects and interim analyses at 30% and 65%, there is 90% power if the true rate in the placebo arm is 4% (corresponding to an absolute difference of 2.4% in rate) and at least 80% power if the true rate in the placebo arm is 3% (corresponding to an absolute difference of 1.8%). Sample size was calculated using SAS (version 9.4) for a 2-sample proportion Chi-square test. Considering a group sequential design with 2 interim analyses and O'Brien-Fleming spending for both alpha (0.025) and beta (0.1), the total sample size was inflated by a multiplier of 1.055 to arrive at a target sample size of 2100 subjects in the supportive-care-only population. Assuming ~95% of randomized subjects in the supportive-care-only population will meet the criteria for inclusion in the mITT-S population , the study targets total enrollment of 2210 subjects in the supportive-care-only population. Planned enrollment in the combination antiviral arm will be up to 300 subjects. Therefore, the total planned sample size will be 2510 subjects. Treatment comparisons and summaries for frequency/proportion secondary endpoints will be similar to those specified for the primary endpoint. Specification of statistical testing for secondary endpoints, with methods used to control overall type I error, will be specified in the SAP. Time-to-event endpoints will be analyzed using Kaplan-Meier methods for estimation and log-rank test for treatment comparison.

	CCI [redacted]

LIST OF ABBREVIATIONS

Term	Definition
AE(s)	Adverse event(s)
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AUC	Area under the curve
AST	Aspartate aminotransferase
AT-527	Bemnifosbuvir hemisulfate; BEM
BAL	Bronchoalveolar lavage fluid
BEM	Bemnifosbuvir hemisulfate
BID	Bis in die; twice daily
BMI	Body mass index
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CoV	Coronaviruses
CRO	Contract research organization
DAIDS	Division of AIDS
DDI	Drug-drug interactions
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
EC_{90}	90% effective concentration
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic Data Capture
ER	Emergency room
ET	Early termination
EU	European Union
EUA	Emergency use authorization
EUL	Emergency use listing procedure
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practices

GI	Gastrointestinal
HCV	Hepatitis C virus
HAE	Human airway epithelia
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intention to treat
IV	Intravenous
mAb	Monoclonal Antibody (ies)
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
MERS	Middle East Respiratory Syndrome
mITT	Modified intention to treat
mITTi	Modified intention to treat infected
mITT-S	Modified intention to treat safety
NiRAN	Nidovirus-RdRP-associated nucleotidyl transferase
NP	Nasopharyngeal
NSAID	Non-steroidal anti-inflammatory drug
Nsp12	Non-structural protein 12
P-gp	P-glycoprotein
PaO_2	Partial pressure of oxygen
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient-reported outcome
PT	Prothrombin time
qPCR	Quantitative polymerase chain reaction
RdRp	RNA-dependent RNA polymerase
RNA	Ribonucleic acid
ROW	Rest of world
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
RT-qPCR	Reverse transcription quantitative polymerase chain reaction
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2

SOC	System organ class
SOP	Standard Operating Procedure
SpO_2	Blood oxygen saturation
TNR	Tumor necrosis factor
ULN	Upper limit normal
US	United States
WBC	White blood cell
WHO	World Health Organization

Principal Investigator PROTOCOL APPROVAL

Protocol Number: *AT-03A-017*

TITLE: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Bemnifosbuvir in High-Risk Outpatients with COVID-19

I have read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with Good Clinical Practices and the applicable regulatory requirements:

_____ _____

Signature
Principal Investigator

Date (dd-mmm-yyyy)

_____

Printed Name
Principal Investigator

1. INTRODUCTION

1.1. Background on COVID-19

Coronaviruses (CoV) are positive-sense, single-stranded RNA viruses, named for the crown-like appearance of their spike glycoproteins on the virus envelope. They are a family of viruses that cause illnesses ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). An epidemic of cases with unexplained lower respiratory tract infections was first detected in Wuhan, the largest metropolitan area in China's Hubei province, and was reported to the World Health Organization (WHO) Country Office in China on 31-Dec-2019. This coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus strain called SARS coronavirus-2 (SARS-CoV-2). The WHO subsequently declared a pandemic on 11-Mar-2020. As of May 20, 2022, over 526 million cases of COVID-19 were reported worldwide, with over 6 million deaths; as of 07 June 2023, over 767 million cases were reported worldwide with over 6.9 million deaths (WHO Dashboard).

Infection with SARS-CoV-2 may be asymptomatic or it may cause a wide spectrum of illnesses, ranging from a mild upper respiratory tract infection to severe life-threatening sepsis and multiorgan failure (Wiersinga et al. 2020). Commonly reported symptoms include fever, cough, shortness of breath, loss of taste or smell, sore throat, fatigue, headaches, muscle aches, and gastrointestinal disturbance. Symptoms are typically thought to last 2 to 3 weeks, but many patients continue to experience symptoms for many weeks or develop new symptoms, which is now recognized as the post-acute COVID-19 syndrome, also called Long COVID (NIHR 2020). COVID-19 affects people of all age; however, people who are elderly or have certain underlying medical conditions (eg obesity, diabetes, chronic heart, lung and kidney disease, and cancer; and the immunocompromised) are at increased risk of mortality and poor outcomes (Carfì et al. 2020; CDC 2022;) and therefore have the greatest unmet need.

Prevention and control of the disease have focused on public health measures to slow transmission, such as social distancing, the use of face masks, national or regional lockdowns, and vaccination. The first of several effective COVID-19 vaccines was authorized in December 2020. However, despite large multi-national vaccination campaigns, as of July 2022, 63% of the global population have been fully vaccinated with rates <40% in many low-income countries; as of March 2023, 67% of the global population have been fully vaccinated with vaccination rates in low-income countries still <40% (New York Times Vaccination Tracker). Furthermore, the durability of response after vaccination is not well understood, and there are known breakthrough infections, including among fully vaccinated individuals, partly driven by the emergence of SARS-CoV-2 variants (Hacisuleyman et al. 2021). COVID-19 vaccines may provide insufficient or incomplete protection due to waning antibody responses post-vaccination. Coupled with the on-going risk of emerging viral variants, the need for additional treatment options is paramount. Additionally, there remains a subset of the population who may not respond to or are ineligible for the available vaccines, have a contraindication to vaccination, or refuse to be vaccinated.

Although access and approvals vary by region, there are a number of therapeutic treatment options for non-hospitalized COVID-19 patients with mild to moderate disease who are at high

risk of disease progression. Depending on the country, Emergency Use Authorization (EUA) or approvals may be available for some of these options, including nirmatrelvir/ritonavir, remdesivir, and molnupiravir. However, there are limitations with all of these compounds, highlighting the need for the continued development of additional novel therapeutics to add to the COVID-19 therapeutic arsenal.

While the efficacy rates for nirmatrelvir/ritonavir are high in high-risk unvaccinated patients (86% reduction in hospitalization/death [Paxlovid. Prescribing Information 2023]), the nirmatrelvir component of nirmatrelvir/ritonavir requires boosting with ritonavir, resulting in significant drug-drug interactions (DDIs). As high-risk patients are likely to be on multiple concomitant medications, this DDI liability has the potential to significantly limit or at least complicate nirmatrelvir/ritonavir's use in the very population for which it is indicated. Before prescribing ritonavir-boosted nirmatrelvir, concomitant medications need to be closely reviewed and potentially managed to prevent serious or life-threatening drug toxicities. Prescribers need to also consider expert consultation, especially for patients receiving highly specialized therapies or drugs prone to concentration-dependent toxicities, such as certain anticonvulsant, anticoagulant, antiarrhythmic, chemotherapeutic, neuropsychiatric, and immunosuppressant drugs. Cases of relapse of symptomatic SARS-CoV-2 infection following suppression with nirmatrelvir and ritonavir have also been reported (Charness et al case report 2022). As more data are gathered in larger populations of patients, it will be important to understand the true incidence and etiology of these relapses in the real-world setting. In addition, the efficacy of nirmatrelvir/ritonavir is decreased in high-risk vaccinated patients (57% reduction in hospitalization/death) as well as standard risk patients (51% reduction in hospitalization/death) [Pfizer press release 2022]).

Similar high efficacy rates were observed with remdesivir (87% reduction in hospitalization/death in high-risk unvaccinated patients). However, remdesivir must be administered intravenously (IV), making it logistically complicated to treat large populations of outpatients who may not have immediate access to dedicated specialized health care facilities with trained health care providers prepared to administer parenteral medications.

Molnupiravir is an orally administered nucleoside analog but has lower efficacy than the preferred treatment options (30% reduction in hospitalization/death in high-risk unvaccinated patients). As a mutagenic ribonucleoside agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations. Molnupiravir is not recommended for use in pregnant patients because fetal toxicity has been reported in animal studies. Also, effective contraception must be used during and following treatment with molnupiravir. In addition, there have been concerns about the potential effects of molnupiravir on SARS-CoV-2 mutation rates. As a result of the above, its use is restricted to only when alternative treatment options are not accessible or clinically appropriate (Lagevrio EUA 2022).

As the effectiveness of the anti-SARS-CoV-2 monoclonal antibody (mAb) therapies varies significantly depending on the circulating variant, the role of each anti-SARS-CoV-2 mAb in the treatment of COVID-19 is dynamic and constantly changing. The use of mAbs is currently limited as the high frequency of circulating SARS-CoV-2 variants are not susceptible to the available mAbs. Like remdesivir, mAbs must also be administered intravenously, making it logistically complicated to treat large populations of outpatients who may not have immediate

access to dedicated specialized health care facilities with trained health care providers prepared to administer parenteral medications and monitor for infusion reactions.

Additional well-tolerated, highly efficacious, more convenient oral, non-mutagenic direct-acting antivirals with a low DDI potential are urgently needed in high-risk patients.

1.2. Background on Bemnifosbuvir

Bemnifosbuvir (AT-527; BEM) is a unique, 6-modified purine nucleotide prodrug discovered by Atea Pharmaceuticals Inc. and does not have a marketing authorization. In laboratory studies, BEM potently inhibits the RNA-polymerase of several single-stranded RNA viruses. BEM is converted to its active intracellular triphosphate form (AT-9010) through a series of intermediate metabolites. AT-9010 binds to the active sites of both RNA-dependent RNA polymerase (RdRp) and nidovirus RdRp-associated nucleotidyl transferase (NiRAN) domains of non-structural protein 12 (nsp12), blocking their respective activities and potently inhibiting SARS-CoV-2 replication via a unique dual mode of action. BEM has demonstrated sub-micromolar potency against a range of coronaviruses, including SARS-CoV-2 (mean 90% effective concentration [EC_{90}] = 0.5 µM). BEM maintains potency *in vitro* against all tested SARS-CoV-2 variants of concern, including Omicron (BA.1, BA.2, BA.4, BA.5 and XBB).

Prior to COVID-19, clinical development for BEM was first initiated for the treatment of chronic hepatitis C virus (HCV) infection. Safety and pharmacokinetic (PK) data (at doses up to 550 mg once daily for up to 12 weeks) from two completed studies within the HCV program (AT-01B-001 and AT-01B-002) supported the clinical evaluation of BEM for COVID-19 at the outset of the pandemic.

As part of an accelerated global clinical development plan in COVID-19, the Phase 2 virology study (WV43042 [MOONSONG]) and the Phase 3 study (CV43043 [MORNINGSKY]) were started in parallel at the end of 2020/beginning of 2021. The CV43043 study was initiated with a 550 mg twice daily (BID) dose of BEM, which was predicted to be the effective dose based on available *in vitro* antiviral activity data, tissue distribution data in animals, and human PK data from healthy subjects and the HCV clinical program. The Phase 2 virology study WV43042 being conducted in parallel was intended to be supportive of the selected dose in CV43043. The initial Phase 3 program objective was to demonstrate alleviation/improvement of COVID-19 symptoms in broad outpatient populations that included both high-risk patients and standard-risk patients (without risk factors). Hospitalization and death were secondary endpoints in CV43043. Of note, the CV43043 study was terminated due to program and operational decisions but there were no safety concerns at the time of discontinuation.

Data from the CV43043 study are available. The encouraging results (described below) support the current Phase 3 study (AT-03A-017).

1.2.1. Summary of Results from the Phase 2 and Phase 3 COVID-19 Studies

The Phase 3 study (CV43043, MORNINGSKY) was a randomized, placebo-controlled study in non-hospitalized adult and adolescent patients with mild or moderate COVID-19 who were at high risk or standard risk for disease progression. The study also allowed vaccinated patients to be enrolled. Patients were randomized (2:1) to receive 550 mg BEM or placebo BID for 5 days. The primary endpoint was time to alleviation/improvement of COVID-19 symptoms. Secondary

endpoints included hospitalization, all-cause mortality and change in viral load. At the time of discontinuation, 216 patients had been randomized (2:1; active:placebo), with 207 patients included in the efficacy evaluable population. The study enrolled a broad outpatient population, with 47% who were high risk, 28% who were vaccinated, and 56% who were seropositive at baseline. Because the study was prematurely discontinued, no formal statistical comparisons were made and results are presented descriptively. Although the primary endpoint of symptoms alleviation or improvement was not met, a lower proportion of patients required hospitalization for COVID-19 (secondary endpoint) in the BEM arm (2.9%; 4/137 patients) compared to the placebo arm (10%; 7/70 patients). This represents a 71% reduction in hospitalization in patients who received BEM. This clinical observation favoring the BEM arm was consistent for the clinical outcome secondary efficacy endpoints, including COVID-19 related medically attended visits (10.2% vs 14.3%; BEM vs placebo), COVID-19 related complications (4.4% vs 10.0%) and post-treatment infections (9.5% vs 14.3%). There were no deaths in the study. There was no meaningful difference in the change from baseline in viral load between the BEM arm and the placebo arm. In addition, the safety and tolerability of the 550 mg BID dose was generally comparable to placebo. There were no drug-related serious adverse events (SAEs) reported, and proportions of patients with adverse events (AEs) leading to study drug discontinuation were low (2.8% in the BEM arm vs 7.0% in the placebo arm). Overall, gastrointestinal (GI) AEs were 11.3% in the BEM arm vs. 9.9% in the placebo arm. There were more drug-related GI AEs (nausea, diarrhea, abdominal discomfort/pain) in the BEM arm (9.2%) compared to placebo (1.4%), but all were low grade (mild/moderate) and none resulted in treatment discontinuation. There was no reported vomiting in the BEM arm.

Although CV43043 was prematurely discontinued and did not meet the primary endpoint of symptom alleviation, the positive signal observed in hospitalization/deaths is the most clinically important and relevant finding to support the Phase 3 AT-03A-017 study. Considering the 71% reduction in hospitalization with BEM was observed in a broad patient population that included vaccinated and standard risk patients, this outcome compares favorably to the rates reported in Phase 3 studies with other oral direct acting antivirals. These other studies enrolled mainly high risk, unvaccinated patients (molnupiravir with a 30% risk reduction; nirmatrelvir/ritonavir with a 86% risk reduction [Paxlovid. Prescribing Information 2023, Lagevrio EUA 2022]). Efficacy with nirmatrelvir/ritonavir was lower in high-risk vaccinated patients (57% risk reduction) and standard risk patients (51% risk reduction) [Pfizer press release 2022]. Although selected as the primary endpoint for the CV43043 study, symptom-based endpoints for COVID-19 will be difficult to achieve considering the variability of presentation across patients, impact of differing and evolving SARS-CoV-2 variants on symptoms, and the lack of validated tools to measure symptoms.

Across the BEM program there have been inconsistent trends with virology data. Despite the observed clinical benefit favoring the BEM arm in the CV43043 study, there was no meaningful difference in nasopharyngeal viral load between the BEM arm and the placebo arm in this study. This lack of correlation is not well understood but is not unique to BEM. Similar findings have been well documented in studies with remdesivir, a United States Food and Drug Administration (US FDA)-approved intravenously administered nucleoside analogue. In the Phase 2 Pinetree study, an 87% reduction in hospitalization/death was observed in high-risk outpatients receiving remdesivir with no impact on viral load (Gottlieb et al 2022) CCI [redacted]

CCI [redacted]

In addition to CV43043, two Phase 2 treatment studies have been conducted, one in an outpatient population (WV43042, MOONSONG) and one in hospitalized patients with moderate COVID-19 (AT-03A-001).

WV43042 was a Phase 2 virology dose-ranging study designed to evaluate the antiviral activity, safety, PK, and efficacy of BEM in non-hospitalized adult patients with mild or moderate COVID-19 who were at high risk or standard risk. The doses evaluated were 550 mg BID and 1100 mg BID for 5 days. The study did not meet its primary virology endpoint of reduction in the amount of SARS-CoV-2 virus RNA by reverse transcriptase polymerase chain reaction (RT-PCR) in the full study population which included a heterogeneous group of low-risk patients who were vaccinated or seropositive at baseline, similar to the CV43043 study population. Nevertheless, there were positive virology trends observed in exploratory subgroups of patients at high risk (SARS-CoV-2 virus RNA reductions by RT-PCR of ~0.5 $\log_{10}$ at Day 7 with BEM [550 mg BID and 1100 mg BID] compared to placebo). The differences in viral load decline in the high-risk cohort were also observed in the infectious virus titer assay. The safety and tolerability of the 550 mg BID dose of BEM was generally comparable to placebo. However, mild to moderate nausea or vomiting led to study drug discontinuation in 16.7% of patients (5 of 30 patients) in the 1100 mg BID arm compared to 0% in the 550 mg BID arm and 2.5% of patients (1 of 40 patients) in the placebo arm.

AT-03A-001 was a prematurely discontinued Phase 2 study designed to evaluate the safety, antiviral activity, and efficacy of BEM in high-risk adult hospitalized patients with moderate COVID-19. Part A of the study evaluated a dose of 550 mg BID for 5 days. Part B was intended to evaluate a dose of 1100 mg BID for 5 days. As with CV43043, this study was also prematurely discontinued due to the changing COVID-19 landscape as management and standard of care for hospitalized COVID-19 patients had adapted making continued enrollment in a placebo-controlled trial no longer feasible in a hospitalized population. Only 2 subjects had been enrolled in Part B and both received placebo. Although low background disease-progression rates precluded achievement of the primary clinical endpoint (protocol-defined progressive respiratory insufficiency), there were numerical trends which directionally favored the BEM 550 mg BID arm. In Part A, the rates of progressive respiratory insufficiency were 7.3% with BEM 550 mg BID (3 of 41 subjects) compared to 10% on placebo (4 of 40 subjects). In addition, the rates of all-cause mortality were 0% with BEM 550 mg BID (0 of 41 subjects) compared to 5% on placebo (2 of 40 subjects). In Part B, a third death occurred in a subject receiving placebo. For the virology endpoints, there were encouraging and consistent trends, similar to those observed in the high-risk subset in the Phase 2 outpatient study. At Day 2, patients receiving BEM 550 mg BID experienced a 0.6 $\log_{10}$ greater mean reduction from baseline viral load as compared to placebo, and a sustained difference in viral load reduction was maintained through Day 8. The safety and tolerability of the 550 mg BID dose of BEM was generally comparable to placebo.

1.2.2. Supportive Results from Clinical Pharmacology and Non-Clinical Studies

Supporting data from a bronchoalveolar lavage (BAL) study in healthy subjects (AT-03A-007) provided confidence that BEM is being efficiently delivered to the lungs (epithelial lining fluid), the primary site of SARS-CoV-2 infection. In this study, it was confirmed that mean levels of BEM above the EC_{90} are achieved in the lungs at 4 hours after dosing with BEM 550 mg BID, with levels of AT-273 that approximate the EC_{90} at 12 hours.

Additionally, the clinical pharmacology of BEM has been investigated in multiple dedicated Phase 1 clinical pharmacology studies. The DDI studies conducted confirm BEM's minimal potential for drug interactions. At doses higher than 550 mg BID, including 825 mg BID and 1100 mg BID, mild to moderate GI-related AEs, specifically nausea and vomiting, and abdominal pain were more frequently reported in healthy subjects (consistent with data from the 1100 mg BID arm of the Phase 2 WV43042 study).

In support of the clinical program, the nonclinical safety profile of BEM was assessed in a comprehensive non-clinical safety program consistent with the requirements set out in the International Conference on Harmonisation (ICH) M3 (R2) guideline and the ICHM3(R2) Q&A (R2) document (ICH 2009; ICH 2012). The intended clinical route of administration (ie oral administration) was used. Rats and monkeys were the selected species for the toxicology and safety pharmacology studies. Both species, as well as the rabbit used in reproductive toxicity studies, convert the prodrug to the active metabolite similarly to humans. Additionally, all metabolites observed in humans were also observed in the preclinical species. BEM is non-mutagenic, has no effect on reproductive performance and is non-teratogenic.

Additional details can be found in the BEM Investigator's Brochure.

1.3. Rationale for the Dose Selection

The dose regimen selected for the current Phase 3 study is 550 mg (2 x275 mg tablets) BID for 5 days, as this dose has shown clinical benefit in CV43043. This dose and duration were well tolerated and resulted in a 71% reduction in hospitalization in the prematurely discontinued Phase 3 study CV43043 in a broad outpatient population, including standard risk and vaccinated patients. Available PK data from this study showed a mean trough of 149.8 ng/mL, right at the targeted 150 ng/mL (based on *in vitro* EC_{90}).

Conceptually, higher doses are expected to achieve higher drug exposure and therefore better clinical outcomes. For BEM, doses beyond 550 mg BID were evaluated in healthy subjects and patients with COVID-19. While, as expected, these studies demonstrated higher AT-273 trough levels of approximately 200 ng/mL with 825 mg BID and 1100 mg BID, these doses were also associated with increased incidences of GI related AEs including vomiting that were not observed in patients with the 550 mg BID regimen. A large phase 1 study (AT-03A-015) was conducted to further investigate the GI AEs for the 825 mg BID regimen. GI AEs including vomiting, while occurring at a lower rate compared with the 1100 mg BID dose (AT-03A-002 cohorts 4 and 5, WV43042 Part B), were still present CCI relative to placebo regardless of meal status.

The 550 mg BID dose was also the initial dose regimen selected for the COVID-19 program based on *in vitro* data, tissue distribution data in non-human primates, and modeling data from

the completed studies in the HCV program. The 550 mg BID regimen was predicted, using plasma AT-273 as a surrogate, to rapidly achieve and maintain a mean intracellular level of the active triphosphate metabolite AT-9010 above the *in vitro* EC_{90} (0.5 uM or 150 ng/mL of AT-273 eq.) of the drug in inhibiting SARS-CoV-2 replication in human airway epithelial (HAE) cells.

Preliminary PK results from the BAL study (AT-03A-007) in healthy subjects demonstrated that antiviral concentrations of AT-273 with the 550 mg BID regimen of BEM were achieved in epithelial lining fluid ELF in the human lung, the primary target of the SARS-CoV-2 virus.

Cumulative PK results from studies in healthy subjects (AT-03A-002) and patients with COVID-19 (AT-03A-001 and WV43042 Part A) have subsequently confirmed that mean plasma concentrations of AT-273 exceeded shortly after dose initiation and maintained mostly above the target of 150 ng/mL during the dosing period of 5 days for the 550 mg BID regimen.

At the 550 mg BID dose, the safety and tolerability of BEM has been generally comparable to placebo. There have been no drug-related SAEs in the program and non-serious AEs have been generally mild to moderate in intensity. No GI-related premature treatment discontinuations have occurred at this dose level in either of the Phase 2 or Phase 3 studies. Overall, over 600 human subjects have been exposed to BEM across both COVID-19 and HCV development programs. Of these, over 350 human subjects have received BEM at or above the selected dose and duration for the Phase 3 study.

1.4. Rationale for Study Population

The COVID-19 landscape is constantly changing and unpredictable, making design of clinical studies challenging. Emerging and evolving SARS-COV-2 variants, waxing and waning of vaccine efficacy over time, differing rates of vaccine booster uptake across populations, differing levels of population immunity, and differing standards of care across geographies are only a few factors that will impact study endpoints and baseline rates of hospitalization and death. Thus, this protocol targets a Phase 3 study population of subjects who are at the highest risk of clinical progression. Age is the strongest risk factor for severe COVID-19 outcomes. As of May 2023, 75% of deaths in the US (>970,000 deaths) occurred in patients ≥65 years of age (CDC Demographic Trends 2023). A consistent trend was observed with BEM in the CV43043 study, in that the hospitalization rates were higher in older patients. In the control arm, the hospitalization rate for subjects > 40 years old was 15.4%, compared to 3.2% for those ≤ 40 years. Further, there was an 82% reduction in risk of hospitalization in the subgroup of patients ≥40 years treated with BEM 550 mg BID. Because age is such a strong risk factor, differing age thresholds are defined in the current protocol, depending on whether patients have concurrent comorbid conditions. The Phase 3 population for this study will include older patients (≥ 70 years or ≥ 55 years with one risk factor or 50 to 54 years with two risk factors) or those ≥ 18 years with other comorbidities (immunocompromised, Down syndrome, sickle cell disease, dementia, Parkinson's disease, or care home residents), regardless of vaccination status. This represents a population of high-risk patients who are in most need of effective COVID-19 treatment options and also are at increased risk of hospitalization/death. Eligibility criteria are generally consistent with the priority list of patients who are at the highest risk of clinical progression according to the NIH COVID-19 Treatment Guidelines as well as those listed by the CDC (NIH 2023, CDC Hospitalization and Death by Age 2023). Studying this enriched high-

risk population is necessary given the relatively low hospitalization/death rate with the current circulating variants.

Enrollment of 24 high-risk adolescents (≥ 12 years to 17 years) will be allowed after the planned interim analysis for which 65% of the supportive-care-only stratum completed the follow-up period (Day 29). A DSMB recommendation that the study continue at this interim analysis point will trigger enrollment of adolescents. Similar safety and PK characteristics are expected for adolescents compared with adults.

1.5. Rationale for Study Design and Allowance of Standard of Care

With the rising COVID-19 cases due to the Omicron variant, more COVID-19 therapies will be required, either as monotherapy or potentially as combination therapy, if resistance and relapse become an issue with current therapies. In the targeted Phase 3 patient population of high-risk patients, SOC for COVID-19 greatly varies globally. While access to antiviral therapies may not be an issue in some countries, their use or access may be limited in other countries. Patients enrolled in the trial will be stratified by SOC type at the time of randomization resulting in two separate strata: those receiving antivirals in addition to study drug (referred to as the "combination antiviral stratum") and those receiving supportive-care-only (no treatments with activity against SARS-CoV-2 except study drug, referred to as the "supportive-care-only stratum"). Functionally, this will result in two distinct populations, one which will allow assessment of BEM as a monotherapy and another that will allow assessment of BEM in combination with other compatible antivirals. It is estimated that the supportive-care-only population will comprise > 88% of the patients enrolled in this global trial. Thus, the primary endpoint, proportion of subjects in the supportive-care-only population who are hospitalized for any cause or who died due to any cause through Day 29, would support a BEM monotherapy indication in this population.

While the primary objective of the study is to demonstrate efficacy in the supportive-care-only stratum (BEM monotherapy), the "combination antiviral stratum" could result in valuable supporting data on the efficacy, antiviral activity, and safety of BEM used in combination with other antiviral drugs. With an expected ~12% of the patients expected to enroll in this stratum, these data collected in parallel could provide the necessary proof-of-concept, hypothesis-generating data to support further evaluations of direct-acting antiviral combination therapy in the targeted population. Considering the speed with which novel SARS-CoV-2 variants are arising and the lack of ability to predict whether currently available therapies will continue to remain effective or whether resistance will develop over time, the study design proactively allows the evaluation of combination therapy CCI [redacted]

This study was designed based on the clinical landscape of COVID-19; no patient groups were consulted in the design of this study.

1.6. Rationale for Primary Endpoint

Rates of hospitalization/death remain the most clinically important and objective endpoints for COVID-19 in the high-risk patient population. One of the most critical goals for the treatment of COVID-19 with a direct-acting antiviral is to reduce the rate of hospitalization or death associated with disease progression via inhibition of SARS-CoV-2 viral replication at the primary site of infection, presumably, the lung. Viral load reduction in nasopharyngeal (NP) swab by reverse transcription quantitative polymerase chain reaction (RT-qPCR) is commonly regarded as a measure of clinical antiviral activity, which is thought to translate into the aforementioned clinical benefits. While this concept has been successful in some cases including the protease inhibitors nirmatrelvir/ritonavir and ensitrelvir, it has not been the case for the nucleotide drug remdesivir. In non-hospitalized patients with COVID-19, remdesivir was able to reduce the risk for hospitalization or death by 87% while showing no difference in viral load reduction compared with placebo (Gottlieb et al., 2022). While the reason for the discordance between clinical antiviral activity measured in NP swab and clinical efficacy/benefits remains to be elucidated, it raises the question on the reliability of using changes in NP swab viral load as a measure of clinical antiviral activity during clinical development of a nucleotide antiviral for SARS-CoV-2. Furthermore, the US FDA *Guidance for Industry COVID-19: Developing Drugs and Biological Products for Treatment or Prevention* (February 2021) acknowledges the lack of established predictive relationship between the magnitude and timing of viral load reductions and the extent of clinical benefit.

The clinical development of BEM for COVID-19, a nucleotide analog belonging to the same class as remdesivir, has largely been focused on demonstrating NP swab viral load reduction. However, virology results have been variable. In the AT-03A-001 phase 2 study in hospitalized patients with moderate COVID-19 and risk factors for poor outcomes, BEM 550 mg BID x 5 days rapidly reduced SARS-CoV-2 viral load with a 0.6 $\log_{10}$ greater mean reduction from baseline as compared to placebo on day 2. A difference in viral load reduction was maintained through Day 8. In the WV43042 phase 2 study in non-hospitalized patients with mild or moderate COVID-19, in the general population overall, BEM 550 mg BID and 1100 mg BID x 5 days did not achieve a statistically significant difference in NP swab viral load reduction from baseline as compared with placebo, although subgroup analyses showed a numerically larger viral load reduction in BEM treated patients with risk factors compared with placebo. Recent data from the prematurely discontinued CV43043 study in patients with mild or moderate COVID-19 seemed partially in agreement with WV43042 in that, in the overall population, BEM 550 BID did not show any difference in NP swab viral load reduction from baseline as compared with placebo. Unlike WV43042, CV43043 did not achieve numerically better viral response in patients with risk factors either. Importantly, BEM 550 mg BID x 5 days substantially reduced the risk of hospitalization by 71% as compared with placebo, in patients without or with risk factors. These analyses support further clinical evaluation of the efficacy of BEM in reducing the rate of hospitalization or death in patients with COVID-19 with virologic responses as secondary/supportive endpoints.

The primary endpoint will be assessed in the supportive-care-only population as the clinical efficacy of BEM can only be evaluated in this population without the interference of the potential clinical benefit provided by the combination with other antivirals. The hospitalization/death endpoint is proposed based on US FDA and other international health

authorities' recommendations and it is most appropriate for a high-risk population such as the one included in this study. It has been the basis for evidence for other authorized and approved therapies in similar populations. As cases continue to rise very rapidly as a result of the current Omicron surge, it remains the most clinically important endpoint for patients, overburdened health care infrastructure, and public health.

1.7. Benefit-Risk Assessment

Overall, BEM was well tolerated across the entire development program. At 550 mg BID in the Phase 2 and CV43043 studies, the safety profile was comparable to placebo. AEs reported were generally mild to moderate in severity and self-limiting. Available data from the BEM clinical pharmacology program suggest a low DDI potential. At dose levels ≥825 mg BID, an increase in GI-related AEs (mostly nausea and vomiting) was observed, which were mild to moderate in severity. GI AEs were more frequent at the 1100 mg BID dose and resulted in early treatment discontinuation. SAEs were only reported in the COVID-19 Phase 2 and Phase 3 studies (none in Phase 1 healthy volunteer studies), assessed as not related to study treatment, and tended to describe progression or complications of COVID-19; SAEs resulting in death have only been reported in subjects receiving placebo. The clinical efficacy data at 550 mg BID from the truncated study CV43043 indicate a benefit in reduction of hospitalizations (71%), COVID-19 complications, and medically attended visits. This clinical benefit was observed consistently across sub-analyses in several populations within the study.

Furthermore, the nonclinical safety profile of BEM was similarly favorable, as assessed in a comprehensive non-clinical safety program. There were no target organs identified in 2- and 13-week toxicity studies. BEM is non-mutagenic, has no effect on reproductive performance and is non-teratogenic.

Based on the totality of the data, BEM at 550 mg BID has demonstrated a favorable benefit-risk profile for evaluation in patients with COVID-19.

2. STUDY OBJECTIVES

The primary objective is:

- To evaluate the efficacy of BEM compared with placebo in reducing all-cause hospitalization or all-cause death in COVID-19 outpatients receiving only supportive care.

The secondary objectives are:

- To evaluate the efficacy of BEM compared with placebo on:
  - COVID-19 related hospitalization or all-cause death through Day 29
  - All-cause death through Day 29 and Day 60
  - COVID-19-related complications (eg., death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, cardiac failure) through Day 29
  - COVID-19-related medically attended visits (hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit) or all-cause death through Day 29 and Day 60
  - COVID-19 symptom relapse
- To evaluate the antiviral activity of BEM compared with placebo on viral load rebound
- To evaluate the safety of BEM compared with placebo

The exploratory objectives are

- To evaluate the efficacy of BEM compared with placebo on:
  - Alleviation or improvement of individual COVID-19 symptoms
  - Return to usual (pre-COVID-19) health
  - Requirement for post-randomization rescue therapy
  - The antiviral activity of BEM compared with placebo
- To assess plasma concentrations of AT-511 (free base form of AT-527 [BEM]) and its metabolites from sparse PK sampling at steady-state

3. STUDY DESIGN

3.1. General Study Design

This Phase 3 randomized, double-blind, placebo-controlled study will be conducted in non-hospitalized adult subjects (≥18 years of age) with mild or moderate COVID-19 (as defined in inclusion criterion 3, Section 4.2) and risk factors for severe COVID-19 (as defined in inclusion criterion 8, Section 4.2).

Age and comorbidities will determine a patient's risk and eligibility (see inclusion criterion 8, Section 4.2). Onset of COVID-19 symptoms will have occurred ≤5 days before randomization.

BEM 550 mg or matching placebo will be administered BID for 5 days (10 doses, with each dose including 2 tablets).

Locally available SOC treatment should be initiated in parallel in addition to study drug (add-on). SOC treatments with direct antiviral activity against SARS-CoV-2 are allowed, but should be initiated during screening and/or within 24 hours prior to or after randomization.

Subjects will be randomized 1:1 (active:placebo) to one of the following arms:

- 550 mg BEM (2 x 275-mg tablets) BID for 5 days
- Placebo (2 tablets) BID for 5 days

Randomization will be stratified by geographic region (North America, Europe, Asia, and rest of world [ROW]), age (< 65 years old vs ≥ 65 years old) and by the type of SOC which the investigator plans to administer in parallel at time of study drug initiation. The type of SOC received will be used to classify subjects into two categories:

a. Combination antiviral stratum (subsequently referred to as the combination antiviral population): In addition to study drug, the subject will be initiated on a local SOC regimen which includes a treatment with direct SARS-CoV-2 antiviral activity. Examples include nirmatrelvir/ritonavir, molnupiravir, favipiravir, mAbs,
b. Supportive-care-only stratum (subsequently referred to as the supportive-care-only population): the SOC regimen the subject will receive does not include any treatment with direct SARS-CoV-2 antiviral activity.

Although randomization is stratified by whether COVID-19 drugs with antiviral effects are administered, both strata allow local SOC therapies without direct antiviral effects (ie corticosteroids).

Patients who require SOC treatment with a non-compatible antiviral treatment, defined as those with a potential DDI with BEM (eg, remdesivir), are excluded.

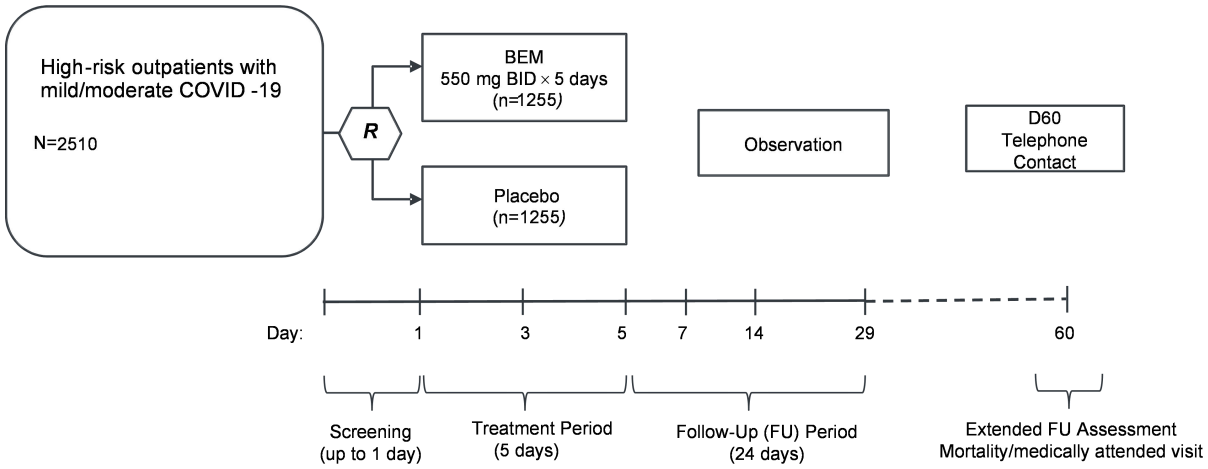
For subjects who deteriorate on-study, any rescue therapy which is SOC for progression to severe COVID-19 is permitted. As noted in Section 5.7.5, if rescue therapy will be remdesivir, study drug should be discontinued before initiation of remdesivir.

Approximately 2510 eligible subjects with COVID-19 will be enrolled, with a target of 2210 subjects in the supportive-care-only population and up to 300 subjects in the combination antiviral population. The primary study endpoint (hospitalization/death) will be evaluated in the supportive-care-only population.

The primary study period is up to 30 days, including up to 1 day for screening and 29 days from randomization. Extended follow-up data will be collected through Day 60 for mortality and medically attended visit assessment. The Day 60 follow-up contact marks the end of study participation for each subject and the study ends when the last subject completes the Day 60 follow-up contact.

A schematic of the study design is presented in Figure 1.

Figure 1: Study Design



This is a global clinical trial that complies with the European Union Clinical Trial Regulations (EU CTR). Results will be released to a publicly accessible web site (eg, Clinical Trial Information System [CTIS]) after the last European subject's completion of the study. However, if the study is ongoing outside the EU as of that date, results will be released after the last subject's completion date.

4. SUBJECT SELECTION

4.1. Study Population

Subjects must meet all the inclusion criteria and none of the exclusion criteria to be eligible for participation in this study.

4.2. Inclusion Criteria

1. Willing and able to provide informed consent.
2. Positive SARS-CoV-2 diagnostic test (RT-PCR or validated rapid antigen test) conducted ≤ 5 days prior to randomization. *Note: The test may be obtained locally. A documented historical record of positive result (RT-PCR or validated rapid antigen test) from test conducted ≤ 5 days prior to randomization is acceptable.*
3. Mild or moderate COVID-19 with symptom onset ≤ 5 days before randomization and at least one COVID-19 related symptom present at time of screening:

- Mild COVID-19:
  - Symptoms of mild illness with COVID-19, which could include fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste or smell, without shortness of breath or dyspnea
  - No clinical signs indicative of moderate, severe, or critical illness severity
- Moderate COVID-19:
  - Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
  - Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, heart rate ≥ 90 beats per minute; with saturation of oxygen (SpO2) > 93% on room air
  - No clinical signs indicative of severe or critical illness severity

4. For females of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for 30 days after the final dose of study drug.
5. Females of childbearing potential must have a negative pregnancy test prior to initiation of study drug.
6. Subject must be able to take oral tablet medications.
7. Subject is, in the opinion of the investigator, willing and able to comply with the study drug regimen and all other study requirements.
8. Subject must be high risk, defined below.

- Age ≥70 years OR
- Age ≥55 years with one of the following risk factors:

- Obesity (body mass index [BMI] ≥30 kg/m^2)
- Diabetes mellitus
- Cardiovascular disease (including congenital heart disease) or hypertension (with at least one medication recommended or prescribed)
- Chronic lung disease requiring routine therapy (eg, chronic obstructive pulmonary disease [COPD], moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)

OR

- Age 50 to 54 inclusive with two of the following risk factors:
  - Obesity (body mass index [BMI] ≥30 kg/m^2)
  - Diabetes mellitus
  - Cardiovascular disease (including congenital heart disease) or hypertension (with at least one medication recommended or prescribed)
  - Chronic lung disease requiring routine therapy (eg, chronic obstructive pulmonary disease [COPD], moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)

  OR

- Age ≥18 years with one of the following:
  - Down syndrome
  - Sickle cell disease
  - Dementia
  - Parkinson's disease
  - Care home residents
  - One of the following immunocompromising conditions or immunosuppressive treatments:
    - On immunosuppressive regimens including chemotherapy for the treatment of cancer
    - Hematologic malignancy associated with poor response to COVID-19 vaccines (eg, CLL, non-Hodgkin lymphoma, multiple myeloma, acute leukemia)
    - Being within 2 years of a hematopoietic stem cell transplant
    - Receipt of a solid-organ transplant and on immunosuppressive therapy
    - Human immunodeficiency virus (HIV) infection (untreated) or with CD4$^+$ T lymphocyte count <350 cells per cubic millimeter (mm^3)
    - Moderate or severe primary immunodeficiency disorder

- Active treatment with an immunosuppressive medication regimen (eg, high-dose corticosteroids [ie, 20 mg of prednisone daily or equivalent for ≥2 weeks], alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents that are severely immunosuppressive, anti-tumor necrosis factor (TNF) blockers, biologics that are immunosuppressive)

- Enrollment of 24 high-risk adolescents (≥ 12 years to 17 years) will be allowed after the planned interim analysis for which 65% of the supportive-care-only stratum completed the follow-up period (Day 29). A DSMB recommendation that the study continue at this interim analysis point will trigger enrollment of adolescents. The Sponsor will notify sites when enrollment of adolescent subjects is permitted. *Note: "High-risk" subjects in this age group are identical to high-risk subjects ≥ 18 years.*

4.3. Exclusion Criteria

1. Female subject is pregnant or breastfeeding.
2. Clinical signs or symptoms indicative of severe or critical COVID-19 illness, including any of the following: shortness of breath at rest, respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air , partial pressure of oxygen/ fraction of inspired oxygen (PaO2/FiO2) <300, shock (defined by systolic blood pressure < 90 mm Hg or diastolic blood pressure < 60 mm Hg or requiring vasopressors), multi-organ dysfunction/failure, respiratory distress, respiratory failure; requirement of endotracheal intubation, mechanical ventilation, oxygen delivered by high-flow nasal cannula, noninvasive positive pressure ventilation, extracorporeal membrane oxygenation (ECMO).

   Note: Subjects receiving chronic supplemental oxygen by nasal cannula are eligible for the study if there has been no increase in baseline oxygen requirement/settings.

3. Admitted to a hospital within 90 days prior to randomization due to COVID-19 or is hospitalized (inpatient) for any reason at randomization.

   Note: If local policy requires COVID-19 isolation or internment in a hospital or similar facility, but subjects otherwise meet criteria, this exclusion may not apply. However, subjects under clinical observation at a clinic/study site or hospital with plans to remain in that setting overnight are not study eligible.

4. In the opinion of the investigator, is likely to experience imminent deterioration and require hospitalization within 24 hours.
5. Use of other investigational drugs within 30 days prior to planned dosing, or plans to enroll in another clinical trial of an investigational agent while participating in the present study, except for unblinded protocols that don't include direct acting antivirals for COVID-19 (eg, open-label oncological regimen variations or biologic studies). Note: Prior to enrolling subjects that are on other open-label studies, it is the site's responsibility to ensure that the study criteria for that study allow for enrollment into this study.

6. Initiation or planned initiation of remdesivir for treatment of the current SARS-CoV-2 infection.
7. Requirement of any prohibited medications, as described in Section 5.7, including either hydroxychloroquine or amiodarone within 3 months prior to screening. (see rationale in Section 5.7.5)
   Note: Subjects who had already initiated any COVID-19 drug with antiviral effects intended to treat symptomatic SARS-CoV-2 infection (≥ 24 hours prior to randomization) will be excluded. During screening (or within 24 hours prior to or after randomization), locally available COVID-19 drugs with antiviral effects (including but not limited to nirmatrelvir/ritonavir, molnupiravir, favipiravir, mAbs) will be permitted, as long as there are no concerns for DDIs (eg, remdesivir would not be permitted).
8. Other known active viral or bacterial infection at the time of screening, such as influenza (ie, as verified by a locally available rapid flu test at screening) or respiratory syncytial virus (RSV).
   Note: This exclusion does not apply to subjects with stable chronic viral infections, such as chronic HCV or HIV providing other eligibility criteria are met.
9. Receiving dialysis or have severe renal impairment [ie estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 within 6 months of the screening visit, using the serum creatinine-based CKD-EPI formula]. Note: If the investigator suspects the subject may have eGFR <30 mL/min/1.73 m^2, a confirmatory test should be performed at screening to confirm eligibility before the first dose of study drug.
10. History of severe hepatic impairment (Child-Pugh Class C)
11. Known allergy or hypersensitivity to components of study drug.
12. Malabsorption syndrome or other condition that would interfere with enteral absorption.
13. Any clinically significant medical condition or known laboratory abnormality that, in the opinion of the investigator, could jeopardize the safety of the subject or impact subject compliance or safety/efficacy observations in the study.

One-time retests of individual screening laboratory parameters or assessments may be permitted in certain scenarios. Such scenarios may include lab processing error, results inconsistent with subject's historical values/medical history, or other extenuating circumstances such as a recent or intercurrent illness potentially affecting screening laboratory results.

5. STUDY TREATMENTS

5.1. Description and Handling of Study Treatments

5.1.1. Test Product

BEM will be provided by the Sponsor as 275 mg tablets (designated as formulation A2-275 mg).

5.1.2. Control Product

Matching placebo tablets for BEM will be provided by the Sponsor.

5.1.3. Packaging and Labeling

The Sponsor will be responsible for ensuring that study drugs (active and placebo) are manufactured in accordance with applicable Good Manufacturing Practice regulations and requirements. The labels for the study drug(s) will meet applicable local regulatory requirements.

5.1.4. Storage and Handling

Study drugs should be stored under the conditions described on the label.

5.1.5. Background Standard of Care

Study drug (BEM or placebo) should be administered as an "add-on" therapy to locally available SOC. Depending on the region, SOC may either include compatible antiviral treatments (such as nirmatrelvir/ritonavir, molnupiravir, favipiravir, mAbs or other COVID-19 drugs with antiviral effects) or alternatively be deemed 'supportive care only' (and not include treatment with COVID-19 drugs with antiviral effects). Standard of care is administered at the discretion of the investigator, based on local practice, and includes therapies or treatments that are locally available to the investigator/site. SOC is not a study drug and is therefore not provided by the Sponsor. However, the type of background SOC that is administered must be documented and captured in the electronic case report form (eCRF).

Patients who require SOC treatment with a non-compatible antiviral treatment, defined as those with a potential DDI with BEM (eg, remdesivir), are excluded.

Auxiliary Medicinal Products (for EU sites)

Compatible antiviral treatments as SOC, such as direct acting antivirals and mAbs, are considered auxiliary medicinal products in this study as per EU regulation No 536/2014 Article 2 (8) and should be used in accordance with the terms of their marketing authorization. Nirmatrelvir/ritonavir is an example of an authorized auxiliary medicinal product. Some compatible antiviral treatments utilized as SOC in the combination antiviral arm of this trial outside of the EU may not be available in the EU; all antivirals will be administered in accordance with their approved local usage.

5.2. Method of Assigning Subjects to Treatment Groups

A unique subject number will be assigned to each subject at screening. Once assigned, it will not be reassigned to another subject. Once eligibility is confirmed, subjects will then be randomly assigned to a treatment group (active vs. placebo) according to a randomization list, generated by the designated independent biostatistician. This will be through a centralized randomization process and eligible subjects may also receive a unique randomization number linked to a treatment assignment. Randomization will be stratified by geographic region (North America, Europe, Asia, and ROW), age (< 65 years old vs ≥ 65 years old) and by the type of SOC which the investigator plans to administer in parallel at time of study drug initiation (combination antiviral vs supportive-care-only). The primary stratification factor is the type of background SOC that the investigator plans to administer as this determines whether the subject is in the supportive-care only group (ie may be included in the primary analysis population) or the combination antiviral group. Within each of the primary strata, randomization is further stratified by geographic region (North America, Europe, Asia, and ROW) and age (<65 and ≥65).

5.3. Blinding

Study site personnel and subjects will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to treatment assignments to fulfill their job roles during a clinical trial. These roles include clinical supply chain managers, any laboratory responsible for performing study drug PK, IxRS service provider, and Data Safety Monitoring Board (DSMB) members.

Unless efficacy is demonstrated at an interim analysis, the study blind will not be broken until after all subjects complete the primary study period (through Day 29).

During the study, the blind may be broken for an individual subject by the investigator only in emergencies or when knowledge of a subject's treatment group is necessary for further subject management. Although not necessary in the case of an emergency, the investigator should discuss the specific case with the Sponsor prior to unblinding. The date and reason for breaking the blind must be recorded.

5.4. Dosing and Administration

5.4.1. Dispensing

Designated site staff will dispense the blinded study drugs (active or placebo) to each subject at the Day 1 visit.

5.4.2. Administration Instructions

Study drug dosing should occur on the same day as randomization. Subjects will self-administer BEM 550 mg (2 x 275 mg tablets) or matching placebo (2 tablets) orally BID on Days 1-5. Each dose consists of 2 tablets. On each dosing day, 2 tablets will be taken for the morning dose and 2 tablets will be taken for the evening dose. The total treatment course consists for a total of 10 doses over 5 days (20 tablets total).

BEM (or matching placebo) should be taken orally approximately 12 hours apart, with a minimum of 6 hours apart. If the first study dose is taken prior to 16:00 on Day 1, the next dose should be taken in the evening of the same day (ie prior to midnight on the same calendar day with a minimum of 6 hours between doses). For these subjects, the final (tenth) dose will be taken in the evening of Day 5. However, if the first study dose is taken after 16:00 on Day 1, the next dose should be taken in the morning of Day 2. For these subjects, the final (tenth) dose will be taken on the morning of Day 6.

BEM (or placebo) tablets should be swallowed whole with a glass of water and should not be chewed, cut, crushed, or dissolved.

If a dose of BEM (or placebo) is missed (ie, not taken within 6 hours after the scheduled dosing time), the subject should resume dosing with the next scheduled dose. Subjects should never double the next dose after a missed dose. In this scenario where a dose is missed, the subject should still complete the full course of 10 doses, making up for the missed dose at the end of the dosing period (as opposed to only taking 9 doses). If a subject vomits after taking a dose, a replacement tablet should not be taken, and dosing should resume with the next scheduled dose. Subjects will be instructed to bring their bottles of study drug to each study visit.

BEM can be taken with or without food.

5.4.3. Treatment Compliance

Subjects will be provided with a dosing diary, to record the times at which they self-administer study drug. The dosing diary will be used to assess treatment compliance. Subjects who have difficulty in using the diary (eg, blind, illiterate, physical limitations, unfamiliar with technology) can obtain assistance from close contacts (eg family members or friends) in recording responses but should not obtain advice or help from others with constructing responses.

5.5. Study Drug Accountability

Complete and accurate records of all study drugs must be kept. These include acknowledgment of receipt of each shipment of study product, subject dispensing records, and records of returned or destroyed study product.

At the end of the study, all unused study drugs and containers will be returned to the Sponsor (or designee) or destroyed, per the instruction of the Sponsor. Documentation confirming drug accountability will be reviewed over the course of the trial.

5.6. Premature Treatment or Study Discontinuation

Subjects may voluntarily discontinue treatment or withdraw from the study at any time. They may also be removed from the study at the discretion of the investigator or Sponsor at any time. The investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject.

Premature treatment or study discontinuation may occur for any of the following reasons:

- Persistent noncompliance with the protocol requirements

- AE
- Death
- Subject request (withdrawal of consent)
- Investigator request
- Sponsor request
- Loss to follow-up
- Pregnancy

Individual Study Drug Stopping Rules

Study drug treatment will be immediately discontinued in any individual subject who experiences:

- Any treatment-emergent SAE, or AE of grade 3 severity or higher (including confirmed laboratory abnormalities of grade 3 severity or higher reported as AEs) considered by the investigator to be related to study drug
- Confirmed estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2
- For subjects with liver function testing within normal limits on the Day 1 lab draw:
    - Confirmed treatment-emergent elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 x ULN with total bilirubin (TB) > 2 x upper limit of normal (ULN) not due to hemolysis, and without evident alternative cause for these elevations
- For subjects with ALT or AST levels above the upper limit of normal on the Day 1 lab draw:
    - Confirmed treatment-emergent elevation of ALT or AST > 3 x baseline with TB > 2 x ULN not due to hemolysis, and without evident alternative cause for these elevations
- For subjects with TB level above the upper limit of normal on the Day 1 lab draw:
    - Confirmed treatment-emergent elevation of ALT or AST > 3 x ULN with TB >2x baseline level (and not due to hemolysis), and without evident alternative cause for these elevations
- Initiation or planned initiation of remdesivir
- Pregnancy

Hospitalization for the acute management of COVID-19 or other medical conditions does not require discontinuation of study drug; however on-going study drug management will be at the discretion of the PI and treating physicians.

Subjects who prematurely discontinue study drug treatment should be encouraged to remain in the study and maintain the same protocol schedule and assessments as described in Table 1. This will allow for continued subject follow-up for key outcome data. Subjects who prematurely

discontinue the study [prior to Day 29 (primary study period)] and are unable to maintain the same protocol schedule should complete early termination (ET) assessments at the time of study discontinuation, as described in Table 1. Nevertheless, all attempts should be made to contact the subject at Day 29 (telephone contact is acceptable) to confirm key study endpoints, including hospitalization and survival.

The primary study period is through Day 29. The end of the study for any individual subject will be defined as the 60-day follow-up contact.

5.7. Prior Therapy, Concomitant Therapy, Permitted Therapy, Cautionary Therapy, and Prohibited Therapy

5.7.1. Prior Therapy

Restrictions on prior therapies are described in exclusion criteria (Section 4.3). Subjects who have used other investigational drugs within 30 days prior to planned dosing (except for exclusions referenced in exclusion criterion #5) or initiated any COVID-19 drug with antiviral effects intended to treat symptomatic SARS-CoV-2 infection ≥ 24 hours prior to randomization will be excluded. Of note, subjects who have received mAb(s) taken as pre- or post-exposure prophylaxis (including if received ≥ 24 hours prior to randomization) will be allowed into the study but they will be considered as part of the combination antiviral cohort.

In addition, hydroxychloroquine or amiodarone within 3 months prior to screening is not allowed for the reasons described in Section 5.7.5.

Subjects may be included regardless of COVID-19 vaccination status. However, information will be collected on timing and type of prior COVID-19 vaccination as well as timing of any prior SARS-CoV-2 infection.

5.7.2. Concomitant Therapy

Concomitant therapy consists of any medication (eg prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject in addition to study drug treatment. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

5.7.3. Permitted Therapy

Locally available SOC treatment should be initiated in parallel in addition to study drug (add-on). If SOC includes treatment that has direct antiviral activity against SARS-CoV-2 (combination antiviral cohort), such drug should be initiated during screening or within 24 hours prior to or after randomization. Allowed SARS-CoV-2 antiviral treatments could include, but are not limited to nirmatrelvir/ritonavir, molnupiravir, favipiravir, and mAbs. SARS-CoV-2 treatments with concerns for DDIs (remdesivir) with BEM are not permitted.

Subjects are also permitted to use the following therapies during the study:

- Acetaminophen (paracetamol)
- Non-steroidal anti-inflammatory drugs (NSAIDs)

- Anti-emetics to manage any nausea or vomiting observed on the study (such as dopamine antagonists, serotonin 5-HT3 receptor antagonists, and antihistamines)
- Prophylactic anticoagulation with low-dose aspirin, direct factor Xa inhibitors, or direct thrombin inhibitors
- Prescribed medications for concomitant conditions as per medical history, such as chronic supplementary oxygen, antihypertensives, antidiabetic medications, rheumatologic medications, or respiratory medications (eg, chronic inhaled/intranasal/oral steroids)
- Hormonal contraceptives (see Section 5.8)
- Hormone replacement therapy
- Corticosteroids
- Convalescent plasma (For purposes of stratification, those receiving convalescent plasma would be included in the supportive-care-only cohort).
- For subjects who deteriorate on-study, any rescue therapy which is SOC for severe COVID-19 is permitted (see Section 5.7.5 for details about remdesivir).

5.7.4. Cautionary Therapy

5.7.4.1. Herbal Therapies

Concomitant use of herbal therapies is not recommended because their PK, safety profiles, and potential DDI are generally unknown.

5.7.4.2. Mitigation of Other Potential DDI

For more details regarding potential DDI, refer to the BEM Investigator's Brochure.

5.7.4.2.1. P-glycoprotein (P-gp)-Based Inhibition

Concomitant use of P-gp inhibitors is permitted but must be taken at least 2 hours after administration of study drug. Common examples of P-gp inhibitors include cyclosporine, carvedilol, imidazoles, macrolides, ritonavir, and verapamil.

For a full list of P-gp inhibitors, refer to: https://go.drugbank.com/categories/DBCAT002667.

Note: As ritonavir is a major P-gp inhibitor, subjects enrolled in the combination antiviral group who are taking nirmatrelvir/ritonavir should not take nirmatrelvir/ritonavir until at least 2 hours after taking study drug.

Subjects taking tacrolimus, sirolimus, or everolimus should do so at least 2 hours after study drug (BEM/placebo).

Subjects taking digoxin must do so at least 2 hours after taking study drug.

5.7.4.2.2. Gastrointestinal Acid Reduction Based Interaction

Gastrointestinal acid reducing agents such as proton-pump inhibitors, H2 blockers and antacids may reduce the solubility of BEM. Subjects taking these agents will do so at least 2 hours after taking study drug.

5.7.4.2.3. Tenofovir Alafenamide

Tenofovir alafenamide and BEM may compete for activation enzymes. Subjects with HIV and/or hepatitis B virus (HBV), who are taking tenofovir alafenamide should do so at least 2 hours after administration of study drug.

5.7.5. Prohibited Therapy

Use of the following concomitant therapies is prohibited from Day 1 until Day 29 (the primary study period) or early termination, except as otherwise indicated, as described below:

- Investigational therapy (other than protocol-mandated study treatment), except for unblinded protocols that don't include direct acting antivirals for COVID-19 (eg, open-label oncological regimen variations or biologic studies)
  Note: Prior to enrolling subjects that are on other open-label studies, it is the site's responsibility to ensure that the study criteria for that study allow for enrollment into this study.
- SARS-CoV-2 treatments with concerns for DDIs: remdesivir
  Note: As BEM and remdesivir share a common target and metabolic activation pathway, there is a potential for PK or pharmacodynamic (PD) drug interactions between the two, during concomitant administration of both drugs. Study drug should be discontinued before initiation of remdesivir.
- Sofosbuvir-containing regimens for subjects with active HCV, as BEM has potent inhibitory activity against HCV, which will cause pharmacodynamic interactions
- Abacavir for subjects with HIV, as abacavir and BEM share a common activation pathway
- Hydroxychloroquine or amiodarone
  Note: There is a known DDI between amiodarone and sofosbuvir (bradycardia). The phosphoramidate moiety of the BEM structure is identical to that of sofosbuvir (SOF). As it is unclear if the phosphoramidate moiety of sofosbuvir is contributory to the DDI, amiodarone use is prohibited to ensure subject safety.

  Coadministration of hydroxychloroquine and remdesivir can result in reduced remdesivir antiviral activity. While remdesivir is not a study drug in this study, it remains a viable rescue therapy that subjects may be given if clinically warranted. Therefore, hydroxychloroquine is prohibited during the study.

5.8. Contraception Requirements

A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than

menopause), and is not permanently infertile due to surgery (ie, removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (eg, Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations. Women of childbearing potential must be established on their chosen method of contraception at screening.

The following are examples of adequate contraceptive methods:

- Bilateral tubal ligation
- Intrauterine device
- Intrauterine hormone-releasing system
- Hormonal contraceptives
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide.
- Vasectomized partner
- Sexual abstinence

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form (ICF).

Should acceptable methods of contraception be more restrictive than the methods listed above per local regulations, guidance, investigator practice, or based on SOC administered (eg, molnupiravir), a more restrictive list may be included within the site/country-specific Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF.

6. STUDY PROCEDURES AND GUIDELINES

Study-specific assessments and the study schedule are summarized in Table 1. An "X" indicates when the assessments are to be performed.

When feasible, visits may be conducted remotely (eg, via telephone or telemedicine), in clinic, or at home.

If possible, screening and Day 1 will occur on the same day, as soon as eligibility is confirmed. Assessments need not be conducted twice if screening/Day 1 occur on the same day. Screening/Day 1 assessments should occur prior to first dose of study drug. Dosing should occur within 24 hours of screening.

The Day 60 visit can be a telephone contact.

All subjects who prematurely discontinue study treatment should be encouraged to remain in the study and maintain the same protocol schedule and assessments as described in Table 1. This will allow for continued subject follow-up for key outcome data. Subjects who prematurely discontinue the study [prior to Day 29 (primary study period)] and are unable to maintain the same protocol schedule should complete early termination (ET) assessments at the time of study discontinuation.

6.1. Schedule of Assessments

The schedule of assessments is provided in Table 1.

Table 1: Schedule of Assessments

	Screening	Treatment			Follow-up (FU)			Extended FU	ET
Day:	**Within 24 hours of dosing**	**1**	**3 (± 1 day)**	**5 (± 1 day)**	**7 (± 1 day)**	**14 (± 1 day)**	**29 (± 1 day)**	**60[a] (± 7 days)**	
ELIGIBILITY									
Informed consent	X								
Demographics	X								
Medical history and baseline conditions	X								
Pre-existing symptom assessment	X								
Rapid test for influenza[b]	X								
PHYSICAL EXAMINATION AND VITAL SIGNS									
Vital signs, including temperature and SpO_2	X	X	X	X	X	X			X
Height and weight	X								
Complete physical examination	X								
Symptom-targeted physical examination		As clinically indicated							X[c]
Assessment of medically attended visit(s)		X	X	X	X	X	X	X	X
LABORATORY									
Central safety lab[d]		X		X		X			X
Pregnancy test (females of childbearing potential)	X								
SARS-CoV-2 diagnostic test, RT-PCR or validated rapid antigen test (obtained locally if needed to confirm eligibility)[e]	X								
Nasopharyngeal (NP) swab (central lab)[f]		X	X	X	X	X	X		X
Blood samples for biomarkers [redacted] CCI [redacted] (central lab)		X		X		X			X
PHARMACOKINETICS									
Plasma sample for sparse PK (central lab)				X					X

	Screening	Treatment			Follow-up (FU)			Extended FU	ET
Day:	**Within 24 hours of dosing**	**1**	**3 (± 1 day)**	**5 (± 1 day)**	**7 (± 1 day)**	**14 (± 1 day)**	**29 (± 1 day)**	**60[a] (± 7 days)**	
STUDY INTERVENTION									
Randomization	X[h]								
Study drug dosing (w/completion of dosing diary)		Days 1–5 (10 doses)							
STUDY ASSESSMENTS									
COVID-19 Symptom Diary		Daily on Days 1–29							
ADVERSE EVENT AND CONCOMITANT MEDICATION MONITORING									
Adverse events (AEs) and concomitant medications	X	X	X	X	X	X	X	SAEs Only	X

[a]Day 60 can be a telephone contact: assessment of mortality and COVID-19 related medically attended visits as defined in Section 6.9
[b] Can be a locally available test and must be negative for the subject to enroll.
[c] As clinically indicated
[d] Safety laboratory tests may be performed at local laboratories if deemed medically necessary by the investigator or Sponsor. In these cases, the site should collect a matching sample and ship it to the central laboratory.
[e]A documented historical positive result from a test conducted ≤ 5 days prior to randomization is acceptable.
[f]Nasopharyngeal swabs should be taken at each visit. Should the subject decline a nasopharyngeal swab, a nasal swab may be collected instead. Collection instructions will be provided by the central lab. In addition to SARS-CoV-2 RT-qPCR and resistance, aliquots may be analyzed for viral titer and other respiratory pathogens such as influenza and RSV to rule out co-infection. For subjects with COVID-19 symptom relapse, NP swabs should also be collected at the time of relapse (see Section 6.6)
[g]Blood samples will be collected. CCI ; others will be kept for future use to potentially analyze disease-related biomarkers or other immune markers to inform the course of the disease.
[h]Study drug dosing should occur on the same day as randomization.
Screening/Day 1 assessments should occur prior to first dose of study drug.
ET = early termination; PK = pharmacokinetics; RT-PCR = reverse transcription polymerase chain reaction

6.2. Medical History

Complete medical history will be obtained at screening. Information about COVID-19 disease history and prior infections, including the onset date of symptoms, and risk factors will be collected. Subjects may be questioned about alcohol and drug use, and information about prior or concomitant medications will also be collected. Information will also be collected on prior COVID-19 vaccine history.

6.3. Physical Examination

A complete physical examination will be performed by a medically qualified individual as scheduled in Table 1. The complete physical examination will include a review of the following: head and neck, ears/nose/throat, lymph nodes, heart, lungs, abdomen, musculoskeletal, neurological, skin, and general appearance.

Demographic data (age, gender, ethnicity/race, body weight, height, BMI) will be recorded.

After screening, a symptom-targeted physical exam should be done as clinically indicated.

6.4. Vital Signs

Vital sign measurements (body temperature, pulse rate, respiratory rate, and blood pressure) and SpO_2 should be captured as specified in Table 1. Vital signs and SpO_2 should be assessed while the subject is in a seated position.

6.5. Safety Laboratory Evaluations

Safety laboratory evaluations will be performed as scheduled in Table 1. The investigator or designee will assess each abnormal value to determine if it is clinically significant.

- Chemistry: Sodium, calcium, potassium, chloride, bicarbonate or total carbon dioxide (either is acceptable), glucose, blood urea nitrogen (BUN) or urea, creatinine, eGFR (CKD-EPI formula), total protein, total bilirubin, direct bilirubin, alkaline phosphatase, AST, ALT, albumin, creatine kinase (CK), triglycerides, cholesterol, amylase, and lipase
- Hematology: White blood cell (WBC) count with differential, red blood cell count, hemoglobin, hematocrit, and platelet count
- Coagulation: Prothrombin time (PT) and International Normalized Ratio (INR)
  Note: Depending on logistics, the laboratory may use the PT to calculate INR and only report the INR to the clinical sites.
- Pregnancy tests (serum or urine) will be performed on female subjects of childbearing potential at screening, as specified in Table 1
  Note, the pregnancy test can be done at Day 1, as long as results are confirmed prior to dosing with study drug.

The total volume of blood withdrawn during the study should not exceed 500 mL. However, it is possible that the total blood donation may be higher if repeat blood samples are required for safety assessments.

6.6. Other Laboratory Evaluations

At screening, a RT-PCR or validated rapid antigen SARS-CoV-2 diagnostic test will be performed locally to confirm eligibility (Table 1). A documented historical positive result from a test conducted ≤ 5 days prior to randomization is acceptable for confirming eligibility.

Samples for the following will be sent to designated central laboratories or Sponsor designee for analysis, on the schedule outlined in Table 1:

- Nasopharyngeal (NP) swab samples for SARS-CoV-2 RT-qPCR; an aliquot will be dedicated for resistance analyses which will be described in a separate resistance monitoring plan. Aliquots may also be analyzed for viral titer and other respiratory pathogens such as influenza and RSV to rule out co-infection
- Blood samples will be collected for potential future biomarker analyses[redacted] others will be kept for future use to potentially analyze disease-related biomarkers or other immune markers to inform the course of the disease.
- Plasma samples for sparse PK analysis

All samples will be processed, stored, and shipped according to the sample processing instructions supplied by the Sponsor or receiving laboratory.

For any subject who experiences a COVID-19 symptom relapse, an NP swab should be collected as soon as possible at the time of symptom relapse. If symptom relapse occurs outside of the planned visit schedule in Table 1, an unscheduled visit should occur to collect the NP swab. Subjects will be instructed to contact their site if they feel their COVID-19 symptom(s) have returned or worsened, after experiencing alleviation or improvement.

6.6.1. Sparse PK Sampling

PK samples will be collected on Day 5, as specified in Table 1, at the same time a blood sample is drawn for safety laboratory analysis. It is important that the date and time of the PK sampling is recorded as well as the date and time of the most recent study drug administration.

6.6.2. Bioanalytical Methods for PK Samples

Plasma concentrations of BEM and metabolites (as appropriate) will be measured according to validated bioanalytical methods.

Samples from all subjects who received at least one dose of BEM will be analyzed. Samples from subjects who received placebo will not be analyzed.

Bioanalytical laboratory personnel will have access to the randomization assignment.

6.7. COVID-19 Symptom Assessment

A COVID-19 symptom diary will be completed daily until Day 29 (Table 1). The symptom diary is provided in Appendix 1 (Section 13.1). This diary will be used to characterize key symptoms recognized as part of COVID-19 illness based on FDA guidance (FDA 2020). The COVID-19

Symptom Diary is composed of individual symptom item questions, each with a 2- or 4- point Likert response option. In addition to symptoms, subjects will be asked for a self-assessment as to whether they have returned to their usual (pre-COVID-19) health status, as well as their assessment of COVID-19 symptom relapse.

On Day 1, a baseline diary questionnaire should be completed at the clinic, prior to the first dose of study drug. Thereafter, the COVID-19 Symptom Diary will be completed in its entirety by the subject once daily at the same time each evening through Day 29.

6.7.1. Data Collection Methods for the PRO

The COVID-19 Symptom Diary is a patient-reported outcome (PRO) measure that will be self-administered at the clinic (Day 1) and/or at home (see schedule in Table 1). At the clinic on Day 1, instruments will be administered before the subject receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

The PRO instrument, translated into the local language as appropriate, will be completed either through use of an electronic application on the subject's own electronic device, through use of a device provided by the Sponsor, or as paper dairy. Subjects should be given the following instructions for completing the PRO at home:

- The assessment should be completed at the same time each day (before bed each evening), and the recall period (in the last 24 hours) should be specified clearly.
- Subjects should complete the instruments in a quiet area with minimal distractions and disruptions.
- Subjects should answer questions to the best of their ability; there are no right or wrong answers.
- Subjects who have difficulty in using the diary (eg, blind, illiterate, physical limitations, unfamiliar with technology) can obtain assistance from close contacts (eg family members or friends) in recording responses, but should not obtain advice or help from others with constructing responses.

During the study visit on Day 1, the PRO instruments should be administered as outlined below:

- Subjects' health status should not be discussed prior to administration of the instruments
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for subjects to complete the instruments
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Subjects should be instructed to answer questions to the best of their ability; there are no right or wrong answers.

- Site staff should not interpret or explain questions but may read questions verbatim upon request.
- Subjects who have difficulty in using the diary (eg, blind, illiterate, physical limitations, unfamiliar with technology) can obtain assistance from close contacts (eg family members or friends) in recording responses but should not obtain advice or help from others with constructing responses.

6.8. Hospitalization

Hospitalization is defined as >24 hours of acute care, in a hospital or similar acute care facility, including Emergency Rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 . This includes specialized acute medical care unit within an assisted living facility or nursing home. This does not include hospitalization for the purposes of public health and/or clinical trial execution. Furthermore, scheduled hospitalization for a pre-planned procedure (including chemotherapy) to treat a pre-existing condition that has not worsened is not an SAE, and would not be considered a hospitalization for the purposes of the efficacy analyses. A pre-existing condition is a clinical condition that is diagnosed prior to the use of study drug and is documented in the subject's medical history.

6.9. COVID-19-Related Medically Attended Visit(s) Assessment

A COVID-19-related medically-attended visit will be defined as follows: hospitalization, (Section 6.8) ER visit, urgent care visit, physician's office visit, or telemedicine visit, with the primary reason for the visit being COVID-19.

Only medically-attended visits related to COVID-19, as determined by the investigator, will be recorded in the eCRF. Details will include at minimum:

- Type of visit (hospitalization, ER, urgent care, physician's office visit, telemedicine)
- Date of visit
- Primary reason for COVID-19 related medically-attended visit
- Treatments given for COVID-19 (including, but not limited to, concomitant medications and supplemental oxygen)
- If hospitalization was required, site personnel will record length of visit, whether intensive care unit (ICU) care was given, or whether mechanical ventilation was required. If additional infectious work-up was performed, the results should be included in the hospitalization narrative.

Any AEs or concomitant therapies reported to the investigator should be recorded on the respective AE eCRF or Concomitant Medications eCRF.

For countries that have local COVID--19 isolation policies, the condition of a medically-attended visit (including hospitalizations) in subjects hospitalized for isolation purposes only would be met either for worsening of disease (such as: AE, treatment, intervention, transfer to higher level of care or as per standard of care would not be an appropriate treatment for an ambulatory

patient) OR subject spontaneously asks for medical advice about their current condition (and confirming the need for advice was important enough that if they were in their home setting, they still would have also sought advice for the same event/concern).

7. ADVERSE EVENTS

7.1. Definitions

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product(s) and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product(s), whether or not considered related to this medicinal product(s).

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug(s) caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug(s) and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug(s).

An AE may be:

- A new illness
- Worsening of a previous chronic illness or a concomitant illness
- An apparent adverse effect of the study medication(s) on safety-related laboratory tests. This observation could include a clinically-significant abnormal laboratory value or a significant shift from baseline (though still within normal range) which the clinical investigator or qualified designate considers to be clinically significant

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned (elective) surgical measures and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the qualified investigator)

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an

SAE, if they meet the definition above. In addition, laboratory or other abnormal assessments (eg, electrocardiogram [ECG], x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described above. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin). Laboratory abnormalities that do not require medical intervention or action are generally not considered AEs.

Severity should be recorded and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017, as described below. If a value falls within the local laboratory normal range, then it will not be graded. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.1.1. Intensity Assessment

The investigator or the designated person will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the subject's eCRF. In classification of AEs, the term "severe" is not the same as "serious". Severity is a description of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "serious" relates to a participant/event outcome or action criteria, usually associated with events that pose an immediate threat to a participant's life or functioning, and meet one or more of the SAE criteria described above.

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 will be used for assessing AEs (DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. [July 2017]). All AEs will be graded as grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (potentially life-threatening), or grade 5 (death) according to the definitions described in the DAIDS Table. Every effort will be made to obtain an adequate evaluation of the severity.

7.1.2. Causality Assessment

The qualified investigator or a medically qualified designate will determine the relationship of any AE to study drugs using the following guidelines in Table 2.

Table 2: Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	There is evidence to suggest a causal relationship between the drug(s) and the AE (eg, AE is uncommon and known to be strongly associated with drug exposure or is uncommon in the study population, but not commonly associated with drug exposure).
No Reasonable Possibility	There is no evidence to suggest a causal relationship between the drug(s) and the AE.

7.2. Routine Reporting

For the purposes of this study, non-serious AEs and SAEs will be recorded in the eCRF from the time of informed consent through Day 29 (the primary study period). SAEs will be recorded through Day 60.

During these periods, all AEs spontaneously reported by the subject, observed by the clinical staff, or elicited by general questioning will be recorded and reported in the eCRF.

Any AE which remains unresolved as of the last visit will require follow-up until the AE has been resolved, a reasonable explanation for its persistence found, or is deemed chronic or stable by the investigator. It is the investigator's responsibility to ensure subjects experiencing AEs receive appropriate follow-up, treatment where required, and that every action is well documented.

Classification will be performed by System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as an SAE or AE in the eCRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF.

7.3. Serious Adverse Event Reporting

Clinical sites must notify CCI of any SAE, without regard to causality, within 24 hours after becoming aware of its occurrence. Any non-serious AE which worsens and eventually meets the criteria for an SAE must also be reported as a new SAE.

Information regarding SAEs will be transmitted to CCI using the Serious Adverse Event form in the electronic data collection tool, which must be completed by a member of the investigational site staff within 24 hours. This form should include a clearly written narrative describing diagnostic terms, signs, symptoms, and treatment of the event; diagnostic procedures; as well as any relevant laboratory data and an assessment of the potential causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (eg an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant information is available.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool and transmit to CCI within 24 hours by one of the following methods:

Email: PPD

Fax: PPD

The site will enter the SAE data into the electronic system as soon as it becomes available.

Contact information for the Sponsor's physician is also listed below, should the sites need to contact the Sponsor to discuss any medical, safety related questions, or SAEs:

PPD

PPD Atea Pharmaceuticals, Inc.

Telephone PPD

Email: PPD

An unlisted (unexpected) SAE is one in which the nature or severity is not consistent with the applicable product reference safety information (RSI). For investigational product(s), the expectedness of an SAE will be determined by whether or not it is listed in the RSI within the Investigator's Brochure(s). Investigators will be notified, and the Investigator's Brochure will be updated, if any new pattern of AEs or laboratory abnormalities is found to be related to BEM dosing.

The start date of an SAE reported on the Serious Adverse Event form must be the same as the start date of the corresponding AE documented on the eCRF. If a change in severity is noted for the existing AE, it must be recorded. If a worsened AE meets the criteria for an SAE, the start date of the SAE must be the same as the start date of the worsened AE.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value is available
- The event can be attributed to agents other than the study drugs or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any SAE reports will be reported by the investigators (or designee) to their local IRB/IEC in accordance with local reporting requirements and reporting timelines.

Similarly, the Sponsor (or designee) will determine whether an SAE must be reported in an expedited manner to regulatory authorities, in accordance with regulatory requirements, including auxiliary medicinal products to Eudravigilance per Directive 2001/83/EC where appropriate. If so, the Sponsor (or designee) will report the event to the regulatory authorities in accord with applicable reporting timelines.

7.4. Pregnancy Reporting

All initial reports of pregnancy in female subjects during the study (until 30 days after the last dose of study drug) or female partners of male subjects, where locally required, must be reported to CCI (see Section 7.3 for contact information) by the investigational staff within 24 hours of their knowledge of the event by completing the "Pregnancy Notification" section of the designated form. All pregnancies will be followed-up to determine the outcome including

spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, maternal and/or newborn complications, or longer where locally required. After the expected pregnancy end date, the site will complete the "Pregnancy Outcome" section of the designated form and provide to the CCI [redacted]. Abnormal pregnancy outcomes are considered SAEs and must be reported using the electronic Serious Adverse Event form. Any subject who becomes pregnant during treatment must immediately discontinue study drug.

8. STATISTICAL ANALYSES

This section summarizes the statistical analyses pertinent to the assessments in this study. A statistical analysis plan (SAP) describing the detailed statistical methods will be developed and finalized before any analyses are performed.

8.1. Analysis Populations

8.1.1. Safety Population

The safety population will include all subjects who received at least one dose of the study drug (BEM or placebo). The study population will be analyzed as treated.

8.1.2. Intention to Treat Population

The intention to treat (ITT) population will include all randomized subjects and will be analyzed as randomized.

8.1.3. Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes all randomized subjects who received ≥1 dose of study drug and have ≥ 1 positive SARS-CoV-2 result (from NP swab samples via central testing) through Day 5. The majority of subjects are expected to have the positive SARS-CoV-2 qualifying sample at baseline, but the window is extended to allow the inclusion of subjects who may have a baseline false negative or missing sample at baseline.

The modified intent-to-treat-S (mITT-S) population includes all randomized subjects who received ≥ 1 dose of study drug, have ≥ 1 positive SARS-CoV-2 result (from NP swab samples via central testing) through Day 5, and who are stratified into the supportive-care-only population.

The modified intent-to-treat-C (mITT-C) population will include all randomized subjects who received ≥ 1 dose of study drug, have ≥ 1 positive SARS-CoV-2 result (from NP swab samples via central testing) through Day 5, and who are stratified into the combination antiviral population.

For analyses and displays based on mITT-S and mITT-C analysis sets, subjects will be classified according to randomized treatment.

8.1.4. PK Population

The PK population will include all subjects who received at least one dose of BEM and for whom evaluable plasma concentration data are available. Subjects who received placebo will not be included in the PK population.

8.2. Endpoints

The primary efficacy endpoint is the proportion of subjects in the supportive-care-only population who are hospitalized for any cause or who died due to any cause through Day 29.

The secondary endpoints are:

Efficacy:

- Proportion of subjects with COVID-19-related hospitalization or who died due to any cause through Day 29
- Proportion of subjects who died due to any cause through Day 29 and Day 60
- Proportion of subjects with COVID-19-related complications (eg., death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, cardiac failure) through Day 29
- Proportion of subjects with COVID-19-related medically attended visits (hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit) or who died due to any cause through Day 29 and Day 60
- Proportion of subjects with COVID-19 symptom relapse (term to be defined in the SAP) through Day 29
- Proportion of subjects with viral load rebound (term to be defined in the SAP) through Day 29

Safety:

- The incidence and severity of adverse events (AEs) and serious adverse events (SAEs)

The exploratory endpoints are:

Efficacy:

- Time to alleviation or improvement of individual COVID-19 symptoms
- Time to self-reported return to usual (pre-COVID-19) health
- Proportion of subjects requiring post-randomization rescue therapy

  Note: For subjects randomized into the combination antiviral population, antiviral medications administered post-baseline within 24 hours of first study drug, as part of the combination regimen, are not considered rescue medication.

  Note: Rescue therapy for the purpose of the endpoint includes only treatments with direct activity against SARS-CoV-2; and that is administered for COVID-19-related clinical decline.
- Duration and severity of COVID-19 symptom relapse
- Proportion of subjects with both COVID-19 symptom relapse and viral rebound
- Change from baseline in amount of SARS-CoV-2 viral RNA as measured by RT-qPCR over time
- Time to cessation of SARS-CoV-2 viral shedding by RT-qPCR

- Proportion of subjects negative for SARS-CoV-2 viral RNA by RT-qPCR over time
- Area under the curve (AUC) in the amount of SARS-CoV-2 viral RNA as measured by RT-qPCR
- Proportion of subjects with treatment-emergent mutations in SARS-CoV-2 viral genes
- CCI [redacted]

Pharmacokinetics:

- Plasma concentrations of AT-511 (free base form of AT-527 [BEM]) and its metabolites

The primary efficacy endpoint will also be assessed in the combination antiviral population as a secondary endpoint. All secondary CCI [redacted] endpoints will be assessed in both the supportive-care-only population, and the combination antiviral population.

8.3. Statistical Methods

The primary and secondary efficacy analyses will be conducted using the mITT-S population. Efficacy analyses will be repeated using the mITT-C population.

Safety analyses will be performed on the safety population, which consists of all subjects who received at least one dose of study drug. In all safety analyses, subjects will be grouped according to the treatment that the subjects actually received rather than the treatment assigned at randomization. Here, treatment will be considered as BEM monotherapy and placebo for subjects in the supportive-care-only population and as BEM combination and compatible antiviral in the combination antiviral population.

Demographics and baseline characteristics will be summarized by treatment group and overall for each analysis population. Disposition, with respect to both treatment and study completion, will be summarized by treatment group and overall with reasons for discontinuation tabulated.

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

Time-to-event endpoints will be analyzed using Kaplan-Meier methods for estimation and log-rank test for treatment comparison.

Data handling for quantitative data that are reported as less than the lower limit of quantification, as well as values reported greater than the upper limit of quantification, will be described in the SAP.

In general, data will be considered as observed, ie, values for missing data will not be imputed.

The primary analysis will occur when all randomized subjects have had sufficient follow-up time to complete the Day 29 visit. Data collected during the extended FU period will be summarized separately, after the primary study analysis.

8.3.1. Primary Efficacy Analysis

The primary efficacy objective of this study is to evaluate the efficacy of BEM based on the proportion of patients who are hospitalized for any cause or who died due to any cause through Day 29 in the supportive-care-only population. The primary estimand is the difference in the proportion of patients who are hospitalized for any cause or who died due to any cause through Day 29 in the supportive-care-only population, and the primary treatment effect comparison will be between the BEM arm and the placebo arm. This proportion will be compared between the BEM and placebo arms using a Cochran-Mantel-Haenszel (CMH) test adjusted for the stratification factors of age and region. The CMH p-value and estimated common risk difference, odds ratio and relative risk, along with the corresponding 95% confidence intervals (CIs) for these estimates, will be presented.

Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. For the intercurrent events of rescue (eg intervention with remdesivir) and concomitant COVID-19 medications, a treatment policy approach will be taken, whereby use of rescue and concomitant medications will be ignored and observations collected after they are administered to the patient will be used. In addition, patients will be followed, assessed, and analyzed irrespective of their completion of the course of the study treatment. The analysis will be performed based on observed data, and the following measures will be used to reduce missing hospitalization/death data: eCRFs capturing clinical information that may be indicative of hospitalization will be reviewed to mitigate the risk of unreported hospitalizations, and study staff may use a public information source to obtain information about survival status if a patient withdraws from the study.

8.3.2. Secondary Efficacy Analyses

Analysis of the primary efficacy endpoint will be conducted for the combination antiviral population as a secondary endpoint. Presentation and analysis of other secondary efficacy endpoints will be carried out using methods similar to those specified for the primary efficacy endpoint. Data handling, analysis populations, and specification of statistical testing for secondary efficacy endpoints, with methods used to control overall type I error, will be detailed in the SAP.

8.3.3. Exploratory Analyses

Additional efficacy and antiviral endpoints will be summarized descriptively. Any exploratory statistical analysis to be conducted on these endpoints will be documented in the SAP.

Resistance analyses, including assessment of treatment-emergent mutations in SARS-CoV-2 viral genes, will be documented in a separate resistance monitoring plan.

CCI [redacted]

Exploratory sub-group analyses may also be conducted; these will be detailed in the SAP.

8.3.4. Safety Analyses

The treatment-emergent period for safety analyses is the time from first study drug administration to Day 29. All lab summaries will be presented by treatment group. Proportions of subjects experiencing treatment-emergent SAEs, AEs, and AEs resulting in treatment discontinuation will be summarized. Adverse event terms will be coded using MedDRA thesaurus terms. Treatment emergent events will be summarized by MedDRA SOC and preferred term, overall and by severity. For subjects experiencing an event with varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Laboratory and vital sign data will also be summarized. Where applicable, laboratory abnormalities will be graded in accordance with the DAIDS severity scale. Shift tables for treatment emergent laboratory abnormalities will be presented.

Study treatment exposure (such as treatment duration and total dose received) will be summarized with descriptive statistics.

8.3.5. PK Analyses

Plasma concentrations of study drug and metabolites in sparse samples will be listed with time data and summarized using descriptive statistics, as applicable.

Additional details regarding safety and PK analyses will be provided in the SAP.

8.4. Interim Analyses

An independent DSMB will evaluate safety, efficacy, and futility, as described in the DSMB charter. Planned interim analyses will include:

- Futility analysis after 30% subjects in the supportive-care-only population are enrolled and have completed the follow-up period (Day 29)
- Interim efficacy, safety, futility analysis) after 65% in the supportive-care-only population are enrolled and have completed the follow-up period (Day 29)

Statistical testing will employ alpha spending and non-binding beta spending, both according to Lan-Demets approximation of O'Brien Fleming method. This controls the overall type I error rate at a one-sided 0.025 level. Total beta spending was specified at a 0.10 level. This corresponds to the following decision criteria

	Nominal p-values for decision	
Analysis	Futility (p > value)	Efficacy (p < value)
Interim 1[a] (30%)	0.8319	[redacted]
Interim 2 (65%)	0.1738	0.0054
Final	0.0233	0.0196
[a] No testing for efficacy will be carried out at Interim 1, but alpha-spending will be employed in accordance with the O'Brien-Fleming spending.		

8.5. Sample Size

The study is powered to detect a true 60% reduction in the hospitalization and all-cause mortality rate with BEM as compared to placebo. With total N=2100 and the interim analysis plan as defined in Section 8.4, there is 90% power if the true rate in the placebo arm is 4% (corresponding to an absolute difference of 2.4% in rate) and at least 80% power if the true rate in the placebo arm is 3% (corresponding to an absolute difference of 1.8%). Sample size was calculated using SAS (version 9.4) for a 2-sample proportion Chi-square test. Considering a group sequential design with 2 interim analyses using both alpha and beta spending according to Lan-Demets approximation of O'Brien Fleming method (see Section 8.4), the total sample size was inflated by a multiplier of 1.055 to arrive at a target sample size of 2100 participants in the supportive-care-only population.

Assuming ~95% of randomized subjects who receive only supportive care as SOC will meet the mITT-S population criteria, the study targets total enrollment of 2210 subjects in the supportive-care-only population. Planned enrollment in the antiviral combination arm is up to 300 subjects.

9. ETHICS

9.1. Institutional Review Board/Independent Ethics Committee

This protocol and the ICF will be submitted to an IRB or IEC prior to initiation of the study and the study will not start until the IRB or IEC, as applicable, has approved the documents.

9.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles in the latest version of the Declaration of Helsinki, the ICH Guideline E6 for Good Clinical Practices (GCP) and local regulations.

9.3. Participant Information and Consent

Before inclusion in the study, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the subject, the subjects will be required to read, sign and date an informed consent form prior to enrollment. Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their ICF.

If an amended or revised ICF is introduced during the study, each subject's further consent must be obtained.

9.4. Subject Confidentiality and Personal Data Protection

The investigators and the Sponsor (and organizations processing data on its behalf [Processers]) will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects should be identified by a unique subject identifier on all study documents provided to the Sponsor (and Processors). In compliance with local regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and IRB/IEC access to review the subject's original medical records for verification of study-related procedures and data.

Supplemental Information for Participating Sites Located in the European Union (EU), as applicable

The collection of data from European patients in the study constitutes a processing of personal data within the meaning of Article 4 of the General Data Protection Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (GDPR).

At an organizational level, to meet European requirements the Sponsor has appointed a certified Data Protection Officer (DPO) in charge of ensuring compliance with data protection regulations. The DPO oversees the conduct of the required Data Protection Impact Assessment (DPIA) to assess and protect rights and freedoms of data subjects regarding processing operations. All Processors are bound by a data protection agreement (DPA). If personal data are transferred to a third country within the meaning of the General Data Protection Regulation (GDPR), the DPA contains the Standard Contractual Clauses established by the European

Commission. The DPO is also in charge of any data subject request and can be contacted directly by the data subject through the email provided in the patient information sheet.

The subjects and healthcare professionals involved in this study will be informed on the type of data collected and processed about them, for which objective and on which legal basis; they will also be informed about their rights on their personal data, and how to exercise their rights.

At a technical level, the Sponsor has implemented and maintains, and requires that Processors have implemented and maintain, measures such that personal data are stored in a secured environment, encrypted, and partitioned from other data. Access to personal data is limited to relevant staff through access policies. All persons accessing data are bound by a confidential clause or professional secrecy.

Subjects will be assigned a unique identifier (data pseudonymization) and will not be identified by name in eCRFs, study databases, study-related forms, study reports, or any related publications. The key to identify subjects is stored in a secure manner by each study site.

The Sponsor will regularly review its technical and organizational security measures and update them to take into account any evolution on technological developments. The Sponsor may apply additional specific statutory requirements, where applicable in the national laws.

Besides technical and organizational measures, the Sponsor, by means of internal measures and imposed contractual clauses to Processors, further maintains the confidentiality of records and personal data of subjects.

The Sponsor has put in place a functional process of reporting of any data breach occurring at the Sponsor's or Processor's facilities and premises which involve personal data of subjects in the clinical study. In case of the occurrence of any data breach, the Sponsor, in consultation with its DPO, will immediately apply relevant measures to mitigate the risks to data subjects as appropriate in relation to the specific context of the data breach, taking into account its source, underlying intentions, possibilities of recovery, etc. Any data breach presenting risks to the rights and freedoms of data subjects will be reported to the relevant supervisory data protection authority within 72 hours of the Sponsor becoming aware of the data breach. In addition, in case of occurrence of a high-risk breach, subjects will be informed by the Sponsor (via clinical study site).

10. DATA COLLECTION, RETENTION, AND MONITORING

10.1. Data Safety Monitoring Board

An independent DSMB will evaluate safety periodically and review unblinded data from interim analyses (Section 8.4), providing any recommendations for early termination or study design adaptations. Timing of additional reviews will be detailed in the DSMB charter.

10.2. Case Report Forms

Designated site staff will use source document entries to enter the data required by the protocol into the eCRFs. Representatives of the Sponsor, the CRO or their designee(s) will train designated site staff on accessing and using a web-based Electronic Data Capture (EDC) system. Investigational site staff will not be given access to the EDC system until the required training is completed and documented. One eCRF will be completed for each subject enrolled in the study. All eCRFs will be reviewed, evaluated, and approved/signed by the investigator (or designee), as required.

The original source documents and a copy of the corresponding eCRFs will be retained by the investigator. Copies of the eCRFs will be provided to the Sponsor (or designee).

10.3. Data Management and Processing

Data from eCRFs and other external data (eg, laboratory data) will be entered into the eCRF or merged with a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

In accordance with the vendor's applicable data management procedures, the clinical database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual checks and listings. Data queries requiring clarification will be issued in the eCRF and sent to the study site for resolution. Only authorized personnel will make corrections to the clinical data in the eCRF, and all corrections will be documented in an audit trail.

10.4. Quality Assurance

This study will be conducted in accordance with standard operating procedures (SOPs) of the CRO(s) that will conduct the study. These SOPs are designed to ensure adherence to ICH Guideline E6 for GCP.

All vendors and clinical sites will be subject to inspection by the Sponsor (or designee) to ensure that the data are generated, documented, and reported in compliance with the study plan and applicable local regulatory requirements.

10.5. Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of

clinical development of the investigational product or at least 25 years after the end of the trial, whichever is longer. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

10.6. Monitoring of the Study

Due to the COVID-19 situation, any training or monitoring described in this section may be conducted remotely or via telephone or video. Depending on the situation over time at each site, it is possible that trainers or monitors may be on-site.

Before study initiation, representatives of the Sponsor or its designee(s) will review the protocol and eCRF with the investigators and their staff and perform study-specific training.

During the study, the study monitor and CRO will check documentation, either remotely or on-site, to ensure completeness of records, accuracy of entries on the eCRFs, adherence to the protocol and to GCP, progress of enrollment, and confirmation study drug supply/logistics. Key study personnel must be available to assist the study monitor during remote or on-site visits.

The investigator must maintain source documents for each subject in the study, which may consist of case and visit notes (hospital or clinic medical records). All information on eCRFs must be traceable to these source documents in the subject's file. For any on-site visits, the investigator must give the study monitor access to any relevant source documents to confirm their consistency with the eCRF entries. The investigator must also keep records documenting the informed consent process. Information in source documents that could identify the subjects (such as the subjects' names) will not be forwarded to the Sponsor (or its designee(s)).

Depending on COVID-19 restrictions, the Sponsor or its representative(s) may visit the study facilities in order to maintain current knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will then permit any trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

11. ADMINISTRATIVE PROCEDURES

11.1. Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety, and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and local regulatory guidelines.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB/IEC for approval.

11.2. Investigator Responsibilities and Delegation of Investigator Duties

The investigator will ensure that all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator will maintain a list of sub-investigators and other appropriately qualified persons to whom he/she delegates significant trial-related duties.

11.3. Premature Termination or Suspension of a Study

The Sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the investigator (or designee) should promptly inform the trial subjects, should assure appropriate follow-up for the subjects, and should inform the regulatory authority(ies)/IRB/IEC, when required.

11.4. Publication Policy

This is a multicenter clinical trial sponsored by Atea Pharmaceuticals. Any formal presentation or publication of data collected for this study will be considered as a joint presentation or publication by the clinical investigator(s) and the Sponsor. As is customary for multicenter trials, publication or presentation of data from individual study centers will not be allowed prior to the publication of the principal study abstract(s) and manuscript(s), without the explicit written permission of Atea Pharmaceuticals. Subsequent publications or presentations of data from the study must receive review and approval from Atea Pharmaceuticals before submission.

Any publication of data generated from this study will adhere to the guidelines delineated in the Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3 (Battisti WP et al 2015). In addition, Atea Pharmaceuticals will determine authorship of the principal study manuscript(s) in accordance with guidance provided by the 2022 ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE). The publication or presentation of any study results shall comply with all applicable privacy laws.

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13. APPENDICES

13.1. Appendix 1: COVID-19 Symptom Diary

COVID-19 Symptom Diary

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.
Note that the following is a sample.

Date of completion:_____ Time of completion:_____

SYMPTOMS

1. Please choose the response below that best describes the worst severity of your COVID-19 symptoms over the past 24 hours.

☐ No symptoms	☐ Mild	☐ Moderate	☐ Severe

2. Please choose the response below that best describes your general physical health over the past 24 hours.

☐ Excellent	☐ Very good	☐ Good	☐ Fair	☐ Poor

3. Have you returned to your usual (pre-COVID) health?

☐ Yes	☐ No

Indicate the worst severity of your symptoms **DURING THE PAST 24 HOURS**

Symptoms	**Absent**	**Mild**	**Moderate**	**Severe**
Cough	☐	☐	☐	☐
Shortness of breath or difficulty breathing	☐	☐	☐	☐
Feeling feverish	☐	☐	☐	☐
Chills	☐	☐	☐	☐
Fatigue (low energy)	☐	☐	☐	☐
Body pain or muscle pain or aches	☐	☐	☐	☐
Diarrhea (loose or watery or more frequent stools)	☐	☐	☐	☐
Nausea (feeling like you want to throw up)	☐	☐	☐	☐
Vomiting (throwing up)	☐	☐	☐	☐
Headache	☐	☐	☐	☐
Sore throat	☐	☐	☐	☐
Nasal obstruction or congestion (stuffy nose)	☐	☐	☐	☐
Nasal discharge (runny nose)	☐	☐	☐	☐

Indicate if you have had the following during the past 24 hours:

	Yes	**No**
Loss of taste	☐	☐
Loss of smell	☐	☐

4. Symptom Relapse: Have your COVID-19 symptoms returned after previously improving?

☐ Yes	☐ No	☐ Not applicable (symptoms have not yet improved)

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