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

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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.

Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory tract infections
Study type	Interventional

Summary

ID

NL-OMON53424

Source
ToetsingOnline

Brief title
AT-03A-017

Condition

- Respiratory tract infections

Synonym
COVID-19, SARS-CoV-2

Research involving
Human

Sponsors and support

Primary sponsor: Atea Pharmaceuticals, Inc.
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: Bemnifosbuvir, COVID-19, SARS-CoV-2

Outcome measures

Primary outcome

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 outcome

• Proportion of subjects in the supportive-care-only population with COVID-19-related hospitalization or who died due to any cause through Day 29

• Proportion of subjects in the overall study population, the supportive care-only population, and the combination antiviral population who died due to any cause through Day 29 and Day 60

• Proportion of subjects in the supportive-care-only population with COVID-19-related complications (e.g., death, hospitalization, radiologically confirmed pneumonia, acute respiratory failure, sepsis, coagulopathy, pericarditis/myocarditis, cardiac failure)

• Proportion of subjects in the supportive-care-only population 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 in each population through Day 29

• Proportion of subjects in each population with viral load rebound through Day

Study description

Background summary

Atea Pharmaceuticals, Inc. is developing BEM, a unique, orally administered 6-modified purine nucleotide prodrug, for the treatment of patients with COVID-19.

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 and there were no safety concerns at the time of discontinuation.

Over 600 human subjects have been exposed to BEM in clinical studies conducted to date, across both COVID-19 and a separate chronic hepatitis C virus development programs. Based on the promising efficacy data from a prematurely discontinued Phase 3 trial CV43043, Atea is advancing the clinical development program for BEM in the treatment of patients with COVID-19.

Study objective

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.

Study design

The study will be conducted in non-hospitalized adult subjects with mild or moderate COVID-19 and risk factors for severe COVID-19. Age and comorbidities will determine a patient*s risk and eligibility. Eligible subjects will include older patients (>= 80 years or >= 65 years with a risk factor) or those >= 18 years with other comorbidities (immunocompromised, Down syndrome, sickle cell disease, dementia, 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. Further rationale for the proposed study population can be found in section 1.4 of the protocol.

Intervention

Eligible subjects will be randomized 1:1 (active:placebo) to one of the following arms:
• 550 mg BEM (2 x 275 mg tablets) BID
• Placebo (2 tablets) BID

BEM 550 mg or matching placebo will be administered BID for 5 days (10 doses, with each dose including 2 tablets). Justification for use of placebo in this study is provided in a separate statement within this application dossier. Locally available standard of care (SOC) should be initiated in parallel in addition to study drug (add-on design).

Study burden and risks

Subject*s participation in this study will last 60 days and consists of a screening period, treatment period, follow up period, and an extended follow-up period. During the treatment period, subjects will need to visit the study site or have a home health visit 3 times in 5 days. During the follow-up period, subjects will need to visit the study site or have a home health visit 3 times in 3 weeks. Extended follow-up data will be collected through Day 60 for mortality and medically attended visit assessment. Aside from the intervention described above, participation in this study involves blood draws and nasopharyngeal swabs at multiple visits.

The nonclinical safety profile of BEM was 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.

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.

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

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 at sea level
- 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 >=80 years OR
• Age >=65 years with one of the following:
- Obesity (body mass index [BMI] >=30 kg/m2)
- Diabetes mellitus
- Cardiovascular disease (including congenital heart disease) or hypertension (with at least one medication recommended or prescribed)
- Chronic lung disease requiring routine therapy (e.g., 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, or care home residents
- One of the following immunocompromising conditions or immunosuppressive treatment:
o Receiving chemotherapy or other therapies for cancer
o Hematologic malignancy (active or in remission)
o Being within 2 years from receiving a hematopoietic stem cell or at any time following a solid organ transplant
o Human immunodeficiency virus (HIV) infection untreated or with CD4+ T

lymphocyte count <350 cells per cubic millimeter (mm3) within the past 6 months
o Combined primary immunodeficiency disorder
o Taking immunosuppressive medications (e.g., drugs to suppress rejection of transplanted organs or to treat rheumatologic and gastrointestinal conditions such as anti-tumor necrosis factor (TNF) agents, mycophenolate, or rituximab)

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 at sea level, 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).
3. Admitted to a hospital within 90 days prior to randomization due to COVID-19 or is hospitalized (inpatient) at randomization due to COVID-19. 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.
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 (e.g., 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 of protocol, including either hydroxychloroquine or amiodarone within 3 months prior to screening. 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 Paxlovid, molnupiravir, favipiravir, mAbs) will be permitted, as long as there are no concerns for DDIs (e.g., remdesivir would not be permitted).

8. Other known active viral or bacterial infection at the time of screening, such as influenza (i.e., 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 HCV or HIV providing other eligibility criteria are met.
9. Receiving dialysis or have known moderate to severe renal impairment [i.e. estimated glomerular filtration rate (eGFR) <45 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 <45 mL/min/1.73 m2, 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.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2023
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Bemnifosbuvir Hemisulfate
Generic name:	Bemnifosbuvir

Ethics review

Approved WMO Date:	21-12-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-05-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-05-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2022-003268-25-NL
ClinicalTrials.gov	NCT05629962
CCMO	NL83271.100.22