# AT-527

# AT-03A-001

# A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF AT-527 IN SUBJECTS WITH MODERATE COVID-19

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|---|---|
| Indication studied: | *COVID-19* |
| Developmental phase of study: | *Phase 2* |
| First subject enrolled: | *09 Sep 2020* |
| Last subject completed: | *28 Feb 2022* |
| Release date of report: | *16 August 2022* |


Company/Sponsor signatory: *Atea Pharmaceuticals*

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This trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

# 2. SYNOPSIS

**Name of Sponsor/Company:**
Atea Pharmaceuticals, Inc.

**Name of Investigational Product:**
AT-527

**Name of Active Ingredient:**
Bemnifosbuvir hemisulfate

**Title of Study:** A Phase 2 randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of AT-527 in subjects with moderate COVID-19

**Study center(s):** [redacted]

**Principal Investigator:** [redacted]
**Investigators:** Refer to Appendix 16.1.4

| **Studied period (years):** | **Phase of development:** 2 |
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| Estimated date first subject enrolled: 09 September 2020<br>Estimated date last subject completed: 28 February 2022 | |

**Objectives:**

**Primary:**

The primary efficacy goal for Part A was to evaluate whether AT-527 significantly reduced progressive respiratory insufficiency (PRI) when compared to placebo.

The primary efficacy goal for Part B was to evaluate whether AT-527 reduced SARS-CoV-2 virus RNA as compared to placebo.

**Secondary:**

The secondary objectives were to evaluate the effects of AT-527 on:

- Reduction in PRI (for Part B only);
- Reduction in SARS-CoV-2 virus RNA (for Part A only);
- Shortening in the median time to clinical recovery by at least 4 days (based on achieving disease resolution in the adapted National Institute of Allergy and Infectious Diseases [NIAID] Clinical Status scale);
- Reducing progression to respiratory failure or death, using the 6-point scale;
- Improving overall clinical status using the NIAID ordinal scale;
- Reducing all-cause mortality;
- Shortening duration of hospitalization for COVID-19;
- Shortening the time to sustained non-detectable SARS-CoV-2;
- Reducing the proportion of subjects who were SARS-CoV-2 positive on Days 5 and Day 14.

**Methodology:**

This was a Phase 2, double-blind, placebo-controlled, randomized treatment study evaluating AT-527 or placebo in combination with supportive standard of care compared with standard of care alone in hospitalized/confined subjects with moderate COVID-19 disease and risk factors for poor outcomes. The study enrolled adults, ≥18 years of age, with moderate COVID-19 and who were not on a ventilator. Subjects must also have had at least one of the known common risk factors for poor

outcomes including obesity (body mass index [BMI] >30), hypertension, diabetes, or asthma. Subjects were documented as SARS-CoV-2 positive in an assay granted Emergency Use Authorization (EUA) by the United States (US) Food and Drug Administration (FDA).

Moderate disease was defined by the following parameters:

- At least one of the following symptoms of COVID-19, with initial symptom onset within 5 days before Screening: fever (> 38.3 °C), cough, sore throat, fatigue/malaise, headache, muscle pain, or more significant lower respiratory symptoms including dyspnea (at rest or with exertion)
- Clinical signs indicative of COVID-19 (as above), with oxygen saturation ($SpO_2$) ≥ 93% on room air or required ≤ 2 L/min oxygen by nasal cannula or mask to maintain $SpO_2$ ≥ 93%.

The study was conducted in 2 parts. Part A evaluated an AT-527 dose of 550 mg twice daily (BID) for 5 days and Part B evaluated a dose of 1100 mg BID for 5 days.

In Part A, subjects were randomized 1:1 to receive AT-527 or placebo approximately every 12 hours for 5 days. A cohort of 20 subjects was initially enrolled to preliminarily assess the safety of the 550 mg BID dosing regimen. Enrollment was paused after the first 20 subjects, until the Data Safety Monitoring Board (DSMB) conducted a safety review. After the DSMB allowed the study to continue without modification, a second cohort of 20 subjects was enrolled in Part A, and enrollment was paused until the DSMB conducted a safety review of these data. The DSMB allowed the study to continue without modification.

An interim analysis was conducted once the first 70 subjects had completed assessments through Day 14. At the time of the interim analysis, 81 subjects had been randomized in Part A. AT-527 at the dose of 550 mg BID was generally well-tolerated and appeared to have antiviral activity in high-risk, hospitalized/confined subjects with moderate COVID-19. At the time of the interim analysis, 1 death in a placebo recipient was reported. There were 6 serious adverse events (SAEs) reported; none were attributed to the study drug.

In Part B, subjects were randomized in a 1:1 ratio to receive either 1100 mg AT-527 or placebo, administered approximately every 12 hours for 5 days for a total of 10 doses. Subjects in both groups were to receive standard of care. Up to 110 subjects were planned to be enrolled in Part B, and an additional DSMB review was planned when 50% of the expected population was enrolled.

**Number of subjects (planned and actual):**

A total of 190 subjects were planned to be enrolled, including 81 subjects in Part A and 110 subjects in Part B.

Shortly after the initiation of Part B, the study was prematurely discontinued due to the changing COVID-19 landscape. Subjects with moderate disease were no longer being hospitalized and those who were had alternative treatment options. As such, enrollment in the study was no longer feasible. At the time of study discontinuation, 81 subjects (41 in the AT-527 group and 40 in the placebo group) had been randomized into Part A and 2 subjects were randomized into Part B (0 in the AT-527 group and 2 in the placebo group).

**Diagnosis and main criteria for inclusion:**

Inclusion criteria included:

1. Willing and able to provide informed consent.
2. Male or female subjects ≥18 years of age.
3. Subject was hospitalized or in a hospital-affiliated confinement facility for which the principal investigator was credentialed and study staff had access to study participants and their data.

4. Subject must have been diagnosed with COVID-19 (SARS-CoV-2 positive) by a standard assay or equivalent testing. *Note: SARS-CoV-2 infection was confirmed with an FDA EUA-approved assay.*
5. Moderate disease defined by the following:
    - At least one of the following symptoms of COVID-19, with initial symptom onset within 5 days prior to Screening: fever (> 38.3 °C), cough, sore throat, fatigue/malaise, headache, muscle pain, or more significant lower respiratory symptoms including dyspnea (at rest or with exertion)
    - Clinical signs indicative of COVID-19 (as above), with $SpO_2 \geq 93\%$ on room air or requires ≤2L/min oxygen by nasal cannula or mask to maintain $SpO_2 \geq 93\%$
6. Subjects must also have at least one of the following known risk factors for poor outcomes: obesity (BMI>30), hypertension, diabetes or asthma.
7. QTcF interval ≤450 ms for males and ≤460 ms for females at Screening.
8. Females of childbearing potential must have agreed to use protocol specified methods of contraception as described in the protocol.
9. Females of childbearing potential must have had a negative pregnancy test at Screening.
10. Subject must have been able to take oral tablet medications.
11. Subject was, in the opinion of the investigator, willing and able to comply with the study drug regimen and all other study requirements.

**Investigational product, dosage and mode of administration:**

In Part A, subjects received oral doses of 550 mg AT-527 or placebo every 12 hours for 5 days.

In Part B, subjects were to receive oral doses of 1100 mg AT-527 or placebo every 12 hours for 5 days.

**Duration of treatment:**

Treatment duration was 5 days.

**Criteria for evaluation:**

The primary analysis for this study was the proportion of subjects who experienced PRI.

**Efficacy:** The efficacy endpoints included:

- PRI, defined as a ≥ 2-tier increase in respiratory support methods required to maintain satisfactory oxygenation (SpO2 ≥ 93%), using a 6-tier hierarchical scale of respiratory support methods within the 14-day study period
- Change from Baseline in quantitative SARS-CoV-2
- Time to clinical recovery
- Proportion of subjects with respiratory failure or death (RFD) by Day 28
- Proportion of subjects improving/worsening from Baseline in clinical status using the NIAID Ordinal Scale by Day 5 and 14
- All-cause mortality
- Duration of hospitalization for COVID-19
- Time to sustained non-detectable SARS-CoV-2
- Time to first SARS-CoV-2 negative test
- Proportion of subjects who were SARS-CoV-2 positive at each time point

**Safety:** Safety assessments included physical examinations, adverse event (AE) monitoring (graded using the World Health Organization toxicity grading guidelines), clinical laboratory tests, and vital signs measurements.

**Statistical methods:**

The primary efficacy endpoint was analyzed using the 6-tier hierarchical scale of respiratory support methods which had the following levels:

- Level 1: Normal oxygenation on room air ($SpO_2$ ≥93), no need for supplemental $O_2$
- Level 2: Persistent hypoxemia on room air ($SpO_2$ <93) with requirement for low-level supplemental $O_2$ by nasal cannula or mask (up to 2L/min) to maintain $SpO_2$ ≥93
- Level 3: Requirement for higher levels of passive supplemental O2 by nasal cannula or mask (≥2 L/min) to maintain $SpO_2$ ≥93
- Level 4: Requirement for oxygenation by positive-pressure devices, e.g., continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) or other non-invasive positive pressure respiratory support methods to maintain satisfactory oxygenation and/or ventilation
- Level 5: Required invasive respiratory support (intubated mechanical ventilation or ECMO)
- Level 6: Death

**Secondary endpoints:**

- A key secondary efficacy endpoint was the change from baseline in amount of quantitative SARS-CoV-2 as measured by RT-PCR on Days 2, 5, and 14. The analyses summarized $log_{10}$ quantitative SARS-CoV-2 at each required scheduled timepoint.
- Clinical recovery was assessed using an adapted NIAID ordinal scale of clinical status and was defined as achievement of disease resolution (status 6, 7, or 8 on the NAID scale). Time to clinical recovery in days on or before Day 14 was defined as:

  Time to clinical recovery by Day 14 (days) = (Date of clinical recovery on or before Day 14 – Date of randomization) +1.

  The median times to clinical recovery were presented for each treatment group as well as the number and percentage of subjects with and without clinical recovery. The Wilcoxon Mann-Whitney test was used to test that there was no difference between the treatment groups by a 1-sided $\alpha$=0.025 p-value.
- The secondary key efficacy endpoint of proportion of subjects with RFD by Day 28 was analyzed similarly to the primary efficacy endpoint. The 1-sided p-value was calculated to test the null hypothesis that the proportion of subjects with RFD on and before Day 28 is less in the treated group. The proportion of subjects with RFD on or before Days 10, 14, and 63 was also analyzed in this manner.
- The secondary endpoint of all-cause mortality was assessed on Days 10, 14, 28 and 63. Subjects who were discontinued from the study for a reason other than death, prior to each of Day 10, 14, 28 and 63 were censored.
- The distribution of subjects improved/the same/worsened from baseline in clinical status was compared between treatment groups on Days 5 and Day 14 with a Mann-Whitney nonparametric test. The lowest observed value on the clinical status (NIAID) scale during Days 1-5 and Days 1-14 was used. The number and percentage of subjects who were "improved", "same", or "worsened" based on their lowest NIAID ordinal scale during these intervals were also presented. The proportion of subjects who died during the study regardless of the cause of death was analyzed in the same manner as the primary efficacy endpoint at Days 10, 14, 28 and 63.

Kaplan-Meier curves (product-limit estimate) were provided by treatment arm for the duration of hospitalization for COVID-19 (days), for the time to sustained non-detectable SARS-CoV-2 (days) and the time to first SARS-CoV-2 negative test (days). Kaplan-Meier estimates of each time were provided at the 25th, 50th (median), and 75th percentiles along with their corresponding 2-sided 95% CIs. The estimates of the SEs were computed using the Greenwood's formula, the CI for the median was calculated according to Brookmeyer and Crowley (Brookmeyer and Crowley 1982), and the CIs for the survival function estimates at each scheduled time point were be derived from the Kaplan-Meier estimates using the log-log transformation.

**Exploratory endpoints:**

- For the time to a NEWS score ≤ 2 endpoint, the median times were presented for each treatment group as well as the number and percentage of subjects who achieved a NEWS score ≤ 2. A Kaplan-Meier curve (product-limit estimate) was provided by treatment arm for the time to a NEWS score ≤ 2 (days).
- COVID-19 symptom resolution was analyzed using the same method as for analysis of NEWS Score ≤2. For COVID-19 symptom severity, a shift from baseline to the worst post-baseline observed severity according to the COVID-19 symptom assessment page of the eCRF by symptom and across all symptoms was presented.
- Change from baseline in C-reactive protein (CRP) and levels of IgG/IgM was presented.
- Change from baseline in the level of SARS-CoV-2 infectious virus titer and percent undetectable were summarized for Days 1, 2, 3, 5, 8, 10, 12, and 14.
- The proportion of subjects with ≥1-tier increased PRI on or before Day 14 was analyzed using the method described for the primary efficacy endpoint.
- For the time-weighted average change from baseline in quantitative SARS-CoV-2, summary statistics were computed for all subjects with baseline data and at least one post-baseline data value within the timeframe over which area under the curve was computed and for each baseline quantitative SARS-CoV-2 subgroup.

**Summary and Conclusion**

**Subject characteristic at Screening:** Demographics were generally comparable between the 2 treatment groups. The overall median age was 56 years, and most subjects (79%) were less than 65 years of age; the placebo group had a slightly higher proportion of subjects who were ≥ 65 years of age. There was a slightly higher proportion of males in the AT-527 group (54%) than in the placebo group (38%). The median body mass index (BMI) at baseline was 30.9 kg/m$^2$ and ranged from 19.9 to 47.3 kg/m$^2$.

**Efficacy results included:**

- The proportion of subjects that experienced PRI was similar for both treatment groups. Due to the overall number of PRI events being lower than expected, no clinically meaningful conclusion could be made.
- A trend in rapid reduction of viral loads was seen in subjects treated with AT-527 as compared to placebo; this was consistent in subjects who had high viral loads at baseline.
- There were no differences observed between the treatment groups in time to clinical recovery.
- Overall, only 1 subject from the placebo group required invasive respiratory support during the study; no subjects in the AT-527 progressed to needing invasive respiratory support.
- Three placebo subjects died during the study including 2 subjects in Part A and 1 subject in Part B. No subjects in the AT-527 group died.

- There were no significant differences between the treatment groups in time to sustained non-detectable SARS-CoV-2 and proportion of subjects with negative SARS-CoV-2 at each time point.

**Safety results:** Overall, 59% of subjects experienced at least 1 TEAE; a similar number of subjects reported TEAEs in both treatment groups. Thirteen percent of subjects experienced treatment-related TEAEs, of which none were Grade ≥3 and 10% of subjects experienced SAEs. In total, 8% of subjects experienced TEAEs leading to study discontinuation, and 3% of subjects in the placebo group experienced TEAEs leading to death.

**Conclusion:** Overall, 550 mg AT-527 did not demonstrate a significant effect on PRI, however, trends in viral load reduction were observed when compared to placebo. AT-527 was well tolerated and showed no deaths, related SAEs, or effects on laboratory and ECG parameters.

**Date of the report: 16 August 2022**