Bemnifosbuvir (AT-527) Treatment of Non-Hospitalized Individuals with Mild-to-Moderate COVID-19: Results from a Truncated Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial (MORNINGSKY)

P2629

Arantxa Horga,[1] Rebecca Saenz,[2] Keith Pietropaolo,[1] Will Stubbings,[3] Neil Collinson,[4] Laura Ishak,[1] Barbara Zrinscak,[5] Bruce Belanger,[1] Catherine Granier,[4] Kai Lin,[1] Aeron C. Hurt,[3] Xiao-Jian Zhou,[1] Steffen Wildum,[3] Janet Hammond[1]

1. Atea Pharmaceuticals Inc., Boston, MA, USA; 2. Genentech Inc., San Francisco, CA, USA; 3. F. Hoffmann-La Roche Ltd., Basel, Switzerland; 4. F. Hoffman-La Roche Ltd., Welwyn Garden City, UK; 5. F. Hoffman-La Roche Ltd., Ontario, Canada.

BACKGROUND

- There remains a need for a safe and efficacious, orally administered, direct-acting antiviral agent, with broad utility for the treatment of COVID-19[1–6]
- Bemnifosbuvir (AT-527) is an oral antiviral guanosine nucleotide analogue that inhibits the viral RNA polymerase, with a unique dual mechanism of action[7]
- In this Phase 3 study (MORNINGSKY; NCT04889040) we aimed to assess efficacy, safety, antiviral activity, and pharmacokinetics (PK) of bemnifosbuvir in nonhospitalized adult and adolescent patients, regardless of vaccination status, with mild-to-moderate COVID-19[8]

METHODS

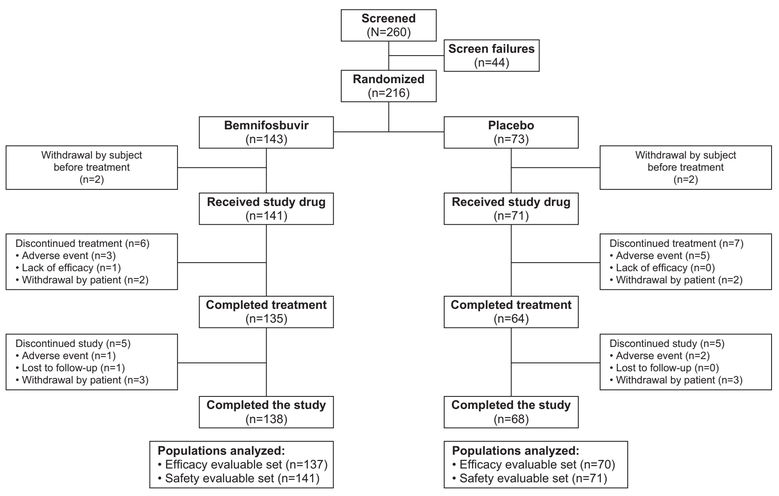
- Eligible patients were adults or adolescents (aged ≥12 years) with mild-to-moderate COVID-19 with or without high-risk factors for hospitalization
  - Symptom onset ≤5 days before randomization was required, with a positive SARS-CoV-2 diagnostic test ≤72 hours before randomization
- Participants were randomly assigned 2:1 to receive oral bemnifosbuvir 550 mg (two 275-mg tablets) or matching placebo tablets BID for 5 days with a 28-day safety and efficacy follow-up period
- The primary efficacy endpoint was time to alleviation/improvement of COVID-19 symptoms maintained for 21.5 hours' duration
  - Defined as either time from randomization to alleviation (i.e., score of 0 or 1 for new symptoms), or time from randomization to symptom maintenance or improvement (for preexisting symptoms) using Items 1–12 of the COVID-19 symptom diary based on a US Food and Drug Administration (FDA) COVID-19 patient-reported outcome instrument
- Key secondary efficacy endpoints included COVID-19 related hospitalization, medically attended visits (MAVs), complications, all-cause mortality, and change in SARS-CoV-2 viral load
- Safety and PK assessments were performed
- Efficacy and virology analyses were performed on the efficacy-evaluable set and the safety analyses used the safety-evaluable set
  - Efficacy-evaluable set: all randomized patients who received ≥1 dose of treatment and were quantitative reverse transcription polymerase chain reaction–confirmed (RT-qPCR) positive for SARS-CoV-2 during the study
  - Safety-evaluable set: all randomized participants who received ≥1 dose of treatment
- Data for each endpoint were analyzed with descriptive statistics by treatment arm and Kaplan–Meier plots, and no formal statistical comparisons were carried out due to the early closure of trial

RESULTS

Patient disposition

- 216 (15.6%) of the 1386 planned patients were randomized

Figure 1. Screening, randomization, and analyses



Baseline characteristics

- Patient baseline characteristics and demographics were generally well balanced between groups, with slight imbalances in patients who were immunocompromised, with a body mass index >30 kg/m², and with more severe Day 1 Patient Global Impression of Severity (PGIS) **(Table 1)**
- Notably, the cohort included both vaccinated and unvaccinated patients, with 40 (29.2%) in the bemnifosbuvir group and 18 (25.7%) in the placebo group vaccinated against COVID-19
- Both treatment groups had patients with high-risk factors, 64 (46.7%) in the bemnifosbuvir group and 33 (47.1%) in the placebo group
- Across treatment groups, 164 patients (87.7%) were infected with the Delta strain

Clinical and virological efficacy

- Bemnifosbuvir did not meet its primary endpoint, with longer median time for symptom alleviation or improvement time than placebo, 3.9 days (94.5 hours) versus 3.1 days (73.7 hours), respectively **(Table 2)**
- For secondary efficacy endpoints, patients receiving bemnifosbuvir experienced lower rates of hospitalizations for COVID-19, COVID-19-related complications, COVID-19-related MAVs, and posttreatment infections compared with placebo **(Figures 2–4)**
  - The relative risk of requiring hospitalization for COVID-19 was 71% lower for those receiving bemnifosbuvir versus placebo (4 [2.9%] vs 7 [10%] patients, respectively)
- In an ad hoc exploratory analysis for patients aged >40 years (MORNINGSKY patients median age, 40 years), bemnifosbuvir reduced relative risk of hospitalization by 82%, compared with a 3% relative risk reduction for patients aged ≤40 years **(Table 2)**
- No clear differences in any of the virology endpoints between the bemnifosbuvir and placebo arms were observed

Safety

- Overall, bemnifosbuvir was well tolerated, with a safety profile comparable with placebo and no new safety signals were observed
- Most adverse events (AEs) were grade 1 or 2, and the most common treatment-related AEs were gastrointestinal **(Tables 3 and 4)**
- AEs leading to treatment discontinuation occurred in 4 (2.8%) patients receiving bemnifosbuvir versus 5 (7.0%) patients receiving placebo
- No deaths were observed during the study

Table 1. Patient demographic and disease characteristics at baseline (efficacy-evaluable set)

Characteristic	Bemnifosbuvir (n=137)	Placebo (n=70)	Total (N=207)
Age, y			
Median (range)	41.0 (15–81)	41.0 (13–91)	41.0 (13–91)
≤40 y, n (%)	65 (47.4)	31 (44.3)	96 (46.4)
>40 y, n (%)	72 (52.6)	39 (55.7)	111 (53.6)
Sex at birth, n (%)			
Male	76 (55.5)	38 (54.3)	114 (55.1)
Race or ethnic group, n (%)			
White	102 (74.5)	47 (67.1)	149 (72.0)
Asian	24 (17.5)	14 (20.0)	38 (18.4)
Hispanic or Latino	38 (27.7)	18 (25.7)	56 (27.1)
Other[a]	11 (8.0)	9 (12.9)	20 (9.7)
BMI, kg/m²			
Median (range)	25.14 (17.4–40.6)	26.62 (16.8–50.8)	25.53 (16.8–50.8)
Smoking history, n (%)			
Nonsmoker	94 (68.6)	40 (57.1)	134 (64.7)
Prior smoker	17 (12.4)	15 (21.4)	32 (15.5)
Current smoker	26 (19.0)	15 (21.4)	41 (19.8)
Presence of high-risk factor, n (%)[b]	64 (46.7)	33 (47.1)	97 (46.9)
Presence of individual adult high-risk factor, n (%)[b]			
	n=64	n=33	N=97
Age (dependent on protocol version)[c]	27 (42.2)	12 (36.4)	39 (40.2)
Obesity (BMI > 30 kg/m²)	23 (35.9)	18 (54.5)	41 (42.3)
Cardiovascular disease	29 (45.3)	18 (54.5)	47 (48.5)
Chronic metabolic disease	14 (21.9)	6 (18.2)	20 (20.6)
Other[d]	11 (17.2)	6 (18.2)	17 (17.5)
SARS-CoV-2 serostatus (spike protein antibody), n (%)			
	n=122	n=58	N=180
Positive	69 (56.6)	32 (55.2)	101 (56.1)
Negative	53 (43.4)	26 (44.8)	79 (43.9)
Severe PGIS on day 1, n (%)	14 (11.6)	1 (1.8)	15 (8.4)
≥1 COVID-19 vaccination dose, n (%)	40 (29.2)	18 (25.7)	58 (28.0)

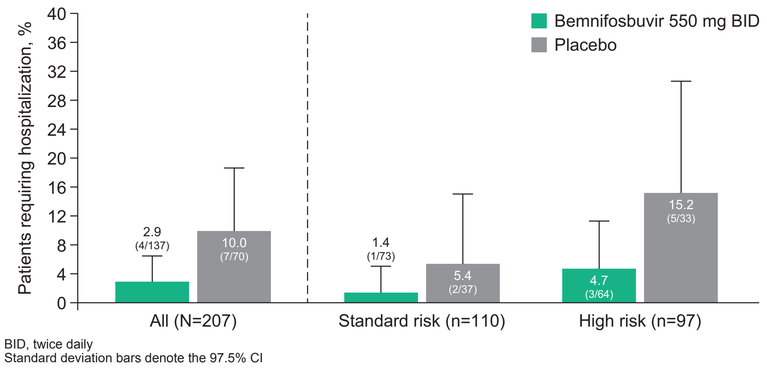
BMI, body mass index; eCRF, electronic case report form; PGIS, patient global impression of severity.
[a]"Other" in race and ethnic groups includes American Indian or Alaska Native, Black or African American, Native Hawaiian or other Pacific Islander. One participant's race and ethnic group was unknown.
[b]Patients may have 1 or multiple high-risk factors.
[c]Presence of a high-risk factor for adult age was defined as >50 years in protocol version 1, and ≥65 years in subsequent protocol versions. Presence of high-risk factor reported as collected in the eCRF.
[d]"Other" in individual high-risk factors includes chronic lung disease, chronic kidney disease, chronic liver disease, and immunocompromised.

Table 2. Summary of the primary and secondary efficacy endpoint results

Key endpoints	Bemnifosbuvir (n=137)	Placebo (n=70)
Primary endpoint: time to symptom alleviation or improvement maintained for ≥21.5 h[a]		
Patients with event, n (%)	128 (93.4)	64 (91.4)
Median time to event,[b] h (97.5% CI)	94.5 (68.1–131.7)	73.7 (47.1–105.8)
Range, h	0–687	0–687
Secondary efficacy endpoints		
Proportion of patients requiring hospitalization for COVID-19		
Patients requiring hospitalization, n (%)	4 (2.9)	7 (10.0)
97.5% CI	0.00–6.51	1.25–18.75
High risk,[c] n (%)	3/64 (4.7%)	5/33 (15.2%)
97.5% CI	0.00–11.39	0.00–30.66
Standard risk,[c] n (%)	1/73 (1.4%)	2/37 (5.4%)
97.5% CI	0.00–5.10	0.00–15.09
Proportion of patients with ≥1 COVID-19-related MAV throughout study		
Patients with ≥1 visit, n (%)	14 (10.2)	10 (14.3)
97.5% CI	4.05–16.38	4.20–24.37
Frequency of COVID-19-related complications		
Patients with complications, n (%)	6 (4.4)	7 (10.0)
97.5% CI	0.10–8.66	1.25–18.75
Proportion of patients with any posttreatment infection		
Patients with posttreatment infection, n (%)	13 (9.5)	10 (14.3)
97.5% CI	3.51–15.47	4.20–24.37
Proportion of patients with all-cause mortality		
Patients with all-cause mortality, n (%)	0	0
Proportion of patients requiring hospitalization for COVID-19 (ad hoc)		
Patients aged ≤40 y, n (%)	2/65 (3.1)	1/31 (3.2)
97.5% CI	0–8.65	0–11.95
Patients aged >40 y, n (%)	2/72 (2.8)	6/39 (15.4)
97.5% CI	0–7.81	1.15–29.62

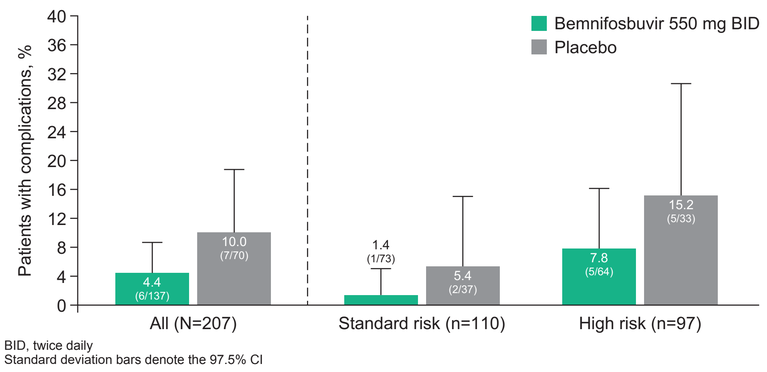
MAV, medically attended visit.
[a]Defined as time from randomization to the first time at which all COVID-19 symptoms from Items 1–12 of the COVID-19 Symptom Diary were either alleviated, maintained, or improved for a minimum duration of 21.5 h.
[b]Median time to event with 97.5% CIs estimated from the Kaplan–Meier curves. 97.5% CI for rates constructed using the Wald with continuity correction method.
[c]Ad hoc analysis.

Figure 2. Rate of hospitalization



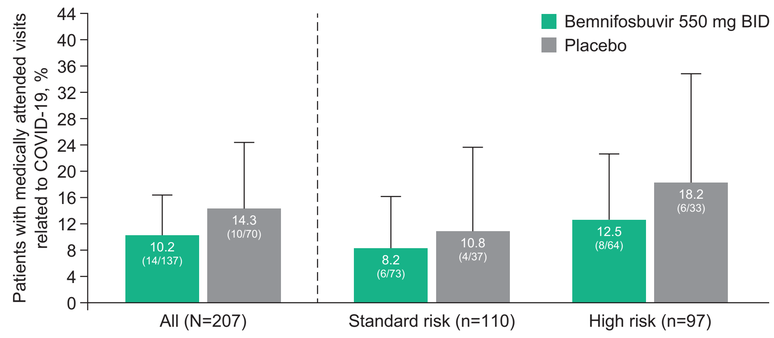
BID, twice daily
Standard deviation bars denote the 97.5% CI

Figure 3. Rate of COVID-19 complications



BID, twice daily
Standard deviation bars denote the 97.5% CI

Figure 4. Rate of MAVs related to COVID-19



BID, twice daily
Error bars denote the 97.5% CI

Table 3. Summary of the AEs in the safety-evaluable set

Category, n (%)	Bemnifosbuvir (n=141)	Placebo (n=71)	Total (N=212)
Total number of AEs[a]	87	51	138
Total number of deaths	0	0	0
Total number of patients who discontinued owing to an AE	1 (0.7)	2 (2.8)	3 (1.4)
Total number of patients with ≥1:			
AE	55 (39.0)	26 (36.69)	81 (38.2)
AE with fatal outcome	0	0	0
Serious AE	7 (9.9)	5 (3.5)	12 (5.7)
Serious AE leading to treatment discontinuation	4 (5.6)	2 (1.4)	6 (2.8)
Treatment-related serious AE	0	0	0
AE leading to treatment discontinuation	4 (2.8)	5 (7.0)	9 (4.2)
Treatment-related AE	21 (14.9)	3 (4.2)	24 (11.3)
Treatment-related AE leading to treatment discontinuation	2 (1.4)	1 (1.4)	3 (1.4)
AE severity (by worst grade)			
Grade 1	23 (16.3)	14 (19.7)	37 (17.5)
Grade 2	27 (19.1)	6 (8.5)	33 (15.6)
Grade 3	4 (2.8)	6 (8.5)	10 (4.7)
Grade 4	1 (0.7)	0	1 (0.7)

AE, adverse event.
[a]Multiple occurrences of the same AE in 1 individual are counted only once except for "Total number of AEs," row in which multiple occurrences of the same AE are counted separately.

Table 4. Summary of AEs in the safety-evaluable set by *MedDRA* system organ class

System organ class preferred term, n (%)	Bemnifosbuvir (n=141)	Placebo (n=71)
Infections and infestations (>5%)	14 (9.9)	10 (14.1)
COVID-19 pneumonia	1 (0.7)	4 (5.6)
Gastrointestinal disorders (>5%)	16 (11.3)	7 (9.9)
Nervous system disorders (>5%)	7 (5.0)	7 (9.9)
Headache	4 (2.8)	5 (7.0)
Musculoskeletal and connective tissue disorders (>5%)	9 (6.4)	3 (4.2)
Back pain	8 (5.7)	0
Skin and subcutaneous tissue disorders (>5%)	5 (3.5)	4 (5.6)
Overall total number of treatment-related events	24	6
Gastrointestinal disorders (>5%)	13 (9.2)	1 (1.4)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

CONCLUSIONS

- Although the MORNINGSKY symptom-based primary endpoint was not met, there was a 71% relative reduction in risk of hospitalization in a broad population with variable disease progression risk
- Bemnifosbuvir had no effect on viral load although there is no firm correlation between viral load reduction and symptom alleviation
- Bemnifosbuvir was well tolerated
- Although truncated, the trends observed in the clinical-based secondary efficacy endpoints warrant further investigation.
- Based on these data, Atea Pharmaceuticals has initiated a global Phase 3 trial (SUNRISE-3; NCT05629962) with an all-cause hospitalization or death primary endpoint in a population at the highest risk for COVID-19 disease progression[9]

References

1. Andrews N, et al. N Engl J Med 2022;386(4):340-350. (In eng). DOI: 10.1056/NEJMoa2115481;
2. Jang EJ, et al. J Med Virol 2022;94(11):5589-5592. (In eng). DOI: 10.1002/jmv.28026;
3. WHO. Therapeutics and COVID-19: Living Guideline. Jan 13, 2023. Accessed Mar 1, 2023. https://app.magicapp.org/#/guideline/nBkO1E;
4. LAGEVRIO. EUA Factsheet. Merck Sharp & Dohme; 2021;
5. PAXLOVID. EUA Factsheet. Pfizer Inc; 2021;
6. NIH. COVID-19 Treatment Guidelines. Dec 28, 2022. Accessed Mar 1, 2023. https://www.covid19treatmentguidelines.nih.gov/tables/variants-and-susceptibility-to-mabs/;
7. Shannon A, et al. Nat Commun 2022;13(1):621. (In eng). DOI: 10.1038/s41467-022-28113-1;
8. ClinicalTrials.gov. NCT04889040. May 17, 2021. Updated Feb 4, 2022. Accessed Mar 1, 2023. https://clinicaltrials.gov/ct2/show/NCT04889040;
9. ClinicalTrials.gov. NCT05629962. Nov 29, 2022. Accessed Mar 1, 2023. https://clinicaltrials.gov/ct2/show/NCT05629962.

Acknowledgments

This study was cosponsored by Atea Pharmaceuticals, Inc and F. Hoffman-La Roche Ltd. Medical writing and design support were provided by Elements Communications Ltd, Westerham, UK and were funded by Atea Pharmaceuticals, Inc.

Disclosures

Arantxa Horga, Keith Pietropaolo, Laura Ishak, Bruce Belanger, Kai Lin, Xiao-Jian Zhou, Janet Hammond are employees of and may own stock in Atea Pharmaceuticals Inc., Boston, MA, USA; Will Stubbings, Neil Collinson, Barbara Zrinscak, Catherine Granier, Aeron C. Hurt, Steffen Wildum, Rebecca Saenz are employees of the Roche Group and may own stock in F. Hoffmann-La Roche Ltd.

Poster presented at the 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2023 Conference 15–18 April, Copenhagen, Denmark