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Short Communication

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Phase II study of bemnifosbuvir in high-risk participants in a hospital setting with moderate COVID-19

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Background: Bemnifosbuvir, a novel, oral, nonmutagenic, nonteratogenic nucleotide analogue inhibits SARS-CoV-2 replication *in vitro*. **Materials & methods:** Adults in hospital settings with moderate COVID-19 were randomized 1:1 bemnifosbuvir/placebo. Study amended to two parts after interim analysis; part B enrollment limited owing to evolving standard of care. **Results:** Although the study ended early and did not meet the primary efficacy end point, bemnifosbuvir was well tolerated and did not contribute to all-cause mortality. Compared with placebo, bemnifosbuvir treatment resulted in 0.61 $\log_{10}$ greater viral load mean change on day 2; trend sustained through day 8. Treatment-emergent adverse events were similar in both groups; most were mild/moderate, unrelated to study drug. **Conclusion:** Our results suggest a potential role for bemnifosbuvir in blunting COVID-19 progression.

Clinical Trial Registration: NCT04396106 (ClinicalTrials.gov)

Tweetable abstract: #Bemnifosbuvir, a novel/oral/nonmutagenic/nonteratogenic/nucleotide analogue with low DDI/resistance potential, inhibits SARS-CoV-2 replication and was well tolerated, did not contribute to all cause mortality and resulted in greater viral load mean change. Results suggest potential to blunt #COVID-19 progression.

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Keywords: AT-527 • bemnifosbuvir • COVID-19 • oral • SARS-CoV-2

The global COVID-19 pandemic began in 2019 following the appearance of SARS-CoV-2 [1]. COVID-19 has posed an overwhelming burden to healthcare systems, especially with cases that require hospitaflization [2]. This pandemic continues to evolve as new variants of SARS-CoV-2 emerge, often featuring increased transmissibility. New variants also pose the threat of developing resistance to current therapies, some of which have already demonstrated decreased efficacy [3].

At the time of this study, recommendations were limited to managing COVID-19 symptoms, as treatments specific for COVID-19 were being tested in clinical trials [4], and vaccines were not yet available [5]. As our study and the pandemic progressed in tandem, COVID-19 management changed owing to alternative treatments being made available, such as the first US FDA-approved antiviral for COVID-19, remdesivir [6], and patients with moderate symptoms were no longer being admitted to hospital settings. Currently, COVID-19 vaccines, including bivalent mRNA vaccines targeting both ancestral and Omicron subvariants, are in use globally [7,8]. Despite these therapeutic advances, waning protection from infection over time remains a significant challenge, and vaccinated individuals may experience breakthrough infections and reinfections [9]. Antiviral agents, including small-molecule inhibitors of main protease/NSP5 (i.e., nirmatrelvir-ritonavir) and RNA-dependent RNA polymerase (RdRp) (i.e., remdesivir, molnupiravir) are widely available, while monoclonal antibodies that block the spike-ACE2 interaction have largely fallen out of use due to the development of resistance [10–12]. Due to the limitations of current antiviral agents including concerns of rebound [13], drug–drug interactions [14] and the potential for mutagenesis [15] and reproductive toxicity [16], new treatment options, including those that are suitable for high risk patients, are urgently needed [11,17]. Oral antiviral agents with novel mechanisms of action may be particularly

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useful [11], as such therapies are convenient and facilitate early treatment of SARS-CoV-2 infection, which can prevent progression to severe disease [18,19].

Bemnifosbuvir hemisulfate (AT-527), an oral antiviral guanosine analogue, inhibits the viral RNA polymerase, an enzyme essential for viral replication. Its unique dual mechanism of action targets the RdRP active site for RNA chain termination, as well as the protein-primed RNA synthesis at the nidovirus RdRP-associated nucleotidyltransferase (NiRAN) active site, which together should decrease the likelihood of simultaneous resistance mutations [20]. Indeed, the free-base form of bemnifosbuvir (AT-511) exhibits potent *in vitro* antiviral activity against variants of concern, including Omicron subvariants [17,21,22]. Further *in vitro* and phase I studies have indicated that bemnifosbuvir has a low risk for drug–drug interactions with medicines commonly taken by high-risk COVID-19 patients for other conditions, including drugs that are sensitive substrates of efflux, hepatic uptake transporters or crucial drug metabolizing enzymes such as CYP3A4 [21,23–25]. Notably, co-medications that are substrates of CYP3A4 may be taken with bemnifosbuvir without dose adjustment as demonstrated in a phase I drug–drug interaction study where plasma levels of a sensitive index substrate of CYP3A4 were not meaningfully altered by bemnifosbuvir [21,23,25]. By contrast, as a strong inhibitor and a substrate of CYP3A4, nirmatrelvir-ritonavir antiviral therapy is contraindicated with drugs that are primarily metabolized by CYP3A and for which elevated concentrations are associated with serious and/or life-threatening reactions, as well as drugs that are strong CYP3A inducers that can significantly reduce nirmatrelvir or ritonavir plasma concentrations. This can lead to potential loss of antiviral activity and possible emergence of resistance [26,27].

The bemnifosbuvir dose evaluated in this study, 550 mg twice daily b.i.d., was based on pharmacokinetics (estimated oral bioavailability of $\geq$50% and a long intracellular $t_{1/2}$ of the active metabolite), which were predicted to achieve lung exposures of the active triphosphate metabolite (AT-9010) consistently above the drug's *in vitro* EC_{90} against SARS-CoV-2 replication [28]. This dose also achieved relevant antiviral drug exposure in the lungs in a separate bronchoalveolar lavage study [29].

We conducted a phase II, randomized, double-blind placebo-controlled study (ClinicalTrials.gov identifier: NCT04396106) to evaluate the safety and efficacy of bemnifosbuvir compared with placebo in high-risk, adult participants with moderate COVID-19 in a hospital setting [30].

Materials & methods

Study population & design

This study was a global, phase II, randomized, double-blind placebo-controlled study [30]. The full protocol and statistical analysis plan are included in the Supplementary Materials. The study was originally planned as a 190-participant study to assess the treatment effect on a primary end point of proportion of subjects with progressive respiratory insufficiency (PRI). A low overall PRI event rate was observed in the blinded aggregate dataset, indicating that it was likely that the initial powering assumptions for the primary end point were no longer reasonable and the study, as originally planned, would be unlikely to provide a sensitive assessment. Consequently, an administrative interim analysis was carried out. Following that analysis, it was decided to stop Part A and continue the study (i.e., Part B; up to an additional 110 participants planned), exploring a higher dose with a change in the primary end point to be based on SARS-CoV-2 virus RNA as measured by RT-PCR on nasopharyngeal swab samples. Eligible participants were adults (aged $\geq$18 years) who were hospitalized or in a hospital-affiliated confinement facility owing to a diagnosis of moderate COVID-19 and $\geq$1 known risk factor for poor health outcomes, including obesity (defined as a body mass index >30), hypertension, diabetes or asthma. Moderate COVID-19 was defined as $\geq$1 of the following symptoms with initial onset $\leq$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) with oxygen saturation $\geq$93% on room air or requiring $\leq$2 l/min oxygen by nasal cannula or mask to maintain. Participants were excluded if they displayed clinical signs indicative of severe or critical COVID-19 [31]. Other key exclusion criteria included evidence of lobar or segmental consolidation, pregnancy or breastfeeding, congestive heart failure or myocardial infarction within previous 6 months, concomitant life-threatening conditions or treatment with a COVID-19 therapeutic agents thought to possibly have activity against SARS-CoV-2 (e.g., antivirals and antibodies).

Randomization & masking

In Part A of this study, participants were randomly assigned (1:1) to receive either oral bemnifosbuvir 550 mg or a matching placebo b.i.d. for 5 days. Participants were stratified at randomization by region. In Part B, participants

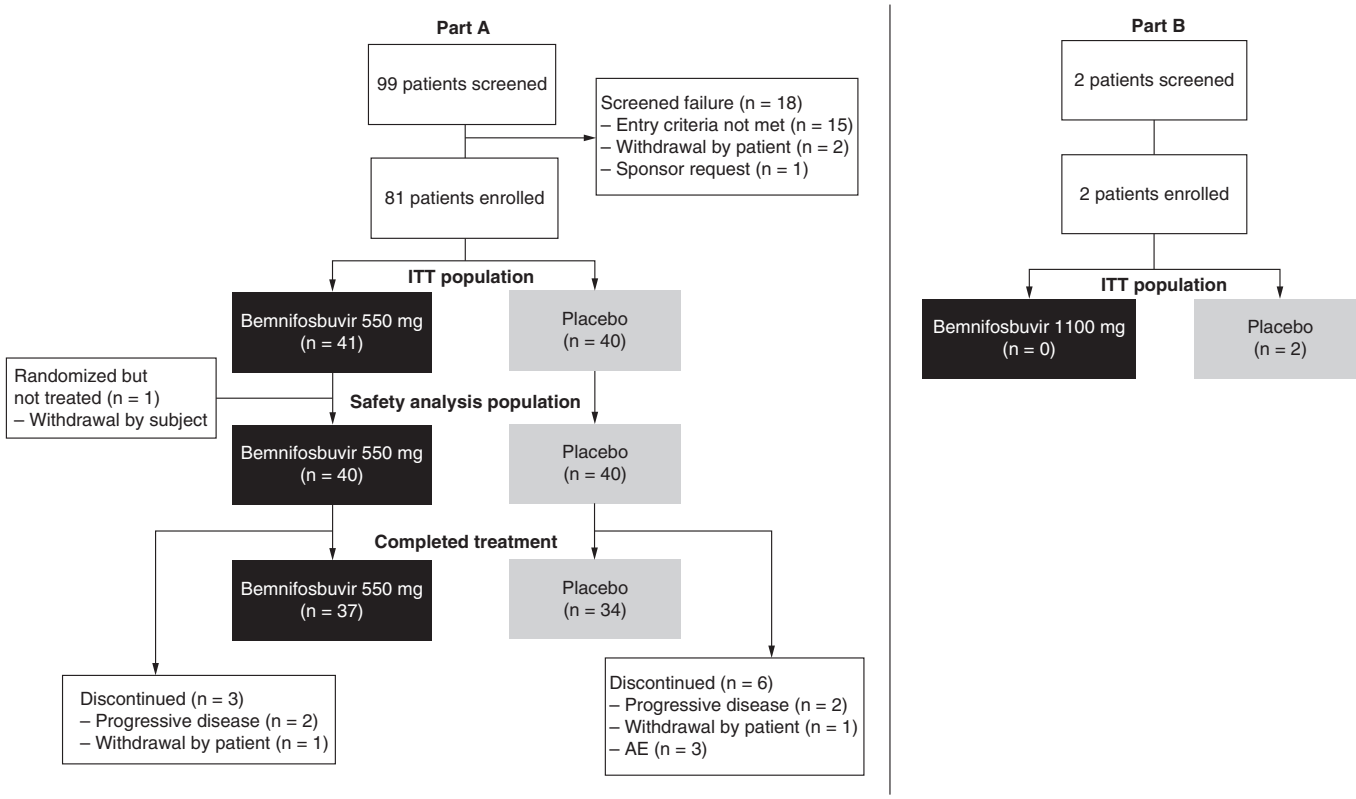

Figure 1. CONSORT diagram.
AE: Adverse event; ITT: Intent-to-treat.

were randomly assigned (1:1) to receive either oral bemnifosbuvir 1100 mg or matching placebo approximately every 12 h for 5 days. Treatment allocation was generated with an interactive response system (voice or web-based) that assigned participants an identification number and treatment assignment. All study site investigators, participants, the Sponsor, research staff and contract research organization personnel were blinded to treatment assignment, except for those who required access to participant treatment assignments for their roles in the study.

End points

Safety end points included adverse events (AEs), serious AEs and treatment-emergent AEs ([TEAEs]; defined as any AE that started or worsened in severity on or after the first dose of study drug but no later than 28 days after the last dose of study drug) leading to discontinuation of the study drug, deaths, blood SpO_2, vital signs, physical examination, electrocardiogram monitoring, standard safety laboratory tests and requirement for mechanical ventilation.

The primary efficacy end point was the proportion of participants with PRI up to day 14. PRI was assessed using the 6-tier scale of increasing levels of respiratory support (Supplementary Table 1) and defined as a ≥2-tier increase in respiratory support interventions to maintain SpO_2 ≥93% over the 14-day study period. The primary efficacy goal was a 50% reduction in the incidence of PRI in participants receiving bemnifosbuvir compared with placebo.

The secondary efficacy end points included the change from baseline in quantitative SARS-CoV-2 virus RNA, all-cause mortality, time to sustained nondetectable SARS-CoV-2 and the proportion of participants who were SARS-CoV-2 positive at days 5 and 14. The secondary end points were to be tested for statistical significance only if the primary efficacy end point met its success criteria and each higher end point met its success criteria to preserve study alpha.

Exploratory objectives included: time to resolution of COVID-19 symptoms, level of SARS-CoV-2 infectious virus titer and monitoring the plasma concentration of bemnifosbuvir and metabolites. Higher viral load may be considered a risk factor for disease progression [32]; therefore, a *post hoc* analysis of key efficacy end points was assessed in participants with baseline viral loads above the median.

Table 1. Participant demographics and disease characteristics at baseline (ITT population).

Characteristic	Bemnifosbuvir 550 mg (n = 41)	Placebo (n = 40)	Total (n = 81)
Age, years			
Mean (SD)	54.3 (11.07)	57.4 (8.33)	55.8 (9.88)
Median (range)	56.0 (23–73)	56.0 (38–74)	56.0 (23–74)
Age group, y, n (%)			
<65	35 (85.4)	29 (72.5)	64 (79.0)
≥65	6 (14.6)	11 (27.5)	17 (21.0)
Sex at birth, n (%)			
Male	22 (53.7)	15 (37.5)	37 (45.7)
Female	19 (46.3)	25 (62.5)	44 (54.3)
Race, n (%)			
White	29 (70.7)	32 (80.0)	61 (75.3)
Black	6 (14.6)	3 (7.5)	9 (11.1)
Asian	2 (4.9)	4 (10.0)	6 (7.4)
Multiple	2 (4.9)	1 (2.5)	3 (3.7)
Not reported	2 (4.9)	0	2 (2.5)
Baseline BMI (kg/m^2)	n = 39	n = 40	n = 71
Mean (SD)	30.7 (6.65)	30.6 (5.18)	30.7 (5.91)
Median (range)	30.90 (20.1–47.3)	30.80 (19.9–46.2)	30.90 (19.9–47.3)
High-risk factors, n (%)	n = 41	n = 40	n = 81
1	16 (39.0)	17 (42.5)	33 (40.7)
>1	25 (61.0)	23 (57.5)	48 (59.3)
Comorbidities, n (%)	n = 35	n = 31	n = 66
1	20 (57.1)	23 (74.2)	43 (65.2)
>1	15 (42.9)	8 (25.8)	23 (34.8)
Obesity at baseline (BMI ≥30 kg/m^2), n (%)	n = 39	n = 40	n = 79
Yes	22 (56.4)	25 (62.5)	47 (59.5)
Hypertension at screening	n = 41	n = 40	n = 81
Yes	30 (73.2)	28 (70.0)	58 (71.6)
Baseline quantitative SARS-CoV-2, log_{10} copies/ml	n = 33	n = 34	n = 67
Mean (SD)	5.34 (1.985)	5.75 (2.024)	5.55 (2.0)
Median (range)	5.42 (2.4–8.6)	5.20 (2.4–8.7)	5.36 (2.4–8.7)

High-risk factors were obesity, hypertension, diabetes and asthma comorbidities at screening.
ITT: Intent-to-treat; SD: Standard deviation.

Assessments

A 6-tier hierarchical scale of respiratory support levels was used to record participant's worsening or improving levels of respiratory insufficiency daily (Supplementary Table 1).

Participants were tested for SARS-CoV-2 by PCR of nasopharyngeal or throat swabs collected throughout the study and performed at a central lab. AEs, defined as new illness, worsening of a previous chronic or concomitant illness or apparent adverse effect of the study medication, were also evaluated daily.

Study protocol and amendments were approved by an Institutional Review Board/Independent Ethics Committee. This trial was sponsored by Atea Pharmaceuticals, Inc, and performed in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline E6 for Good Clinical Practices and local regulations. All participants or their legal representative provided written, informed consent to participate.

Statistical methods

Each end point reported in this manuscript was analyzed with descriptive statistics by treatment arm. The Cochran–Mantel–Haenszel test was performed to compare the proportion of participants with PRI in study arms. Assuming rates of 0.4 and 0.2 in the placebo and experimental arms, respectively, and testing at alpha 1-sided of 0.025 with power of 0.8, a total of 182 participants were required at a 1:1 allocation (i.e., 91 per study arm). However, this

Table 2. Summary of treatment-emergent adverse events (> %) in the safety-evaluable set.

Category	Bemnifosbuvir 550 mg (n = 40)	Placebo (n = 40)	Total (n = 80)
Subjects with ≥1 TEAE, n/n (%)	24/40 (60)	23/40 (58)	47/80 (59)
Subjects with ≥1 TEAE with grade ≤3 severity, n/n (%)	5/40 (13)	6/40 (15)	11/80 (14)
Treatment-emergent serious adverse event, n/n (%)	5/40 (13)	3/40 (8)	8/80 (10)
TEAE leading to permanent discontinuation of study drug, n/N (%)	2/40 (5)	4/40 (10)	6/80 (8)
TEAE leading to death, n/N (%)	0	2/40 (5.0)	2/80 (3)
TEAEs by SOC and preferred term (>5%), n/n (%)			
Cardiac disorders	2/40 (5)	1/40 (3)	3/80 (4)
Sinus tachycardia	2/40 (5)	0	2/80 (3)
Gastrointestinal disorders	5/40 (13)	9/40 (23)	14/80 (18)
Diarrhea	2/40 (5)	3/40 (8)	5/80 (6)
Enterocolitis	2/40 (5)	1/40 (3)	3/80 (4)
Flatulence	1/40 (3)	2/40 (5)	3/80 (4)
Constipation	0	2/40 (5)	2/80 (3)
Nausea	0	2/40 (5)	2/80 (3)
General disorders and administration site conditions	2/40 (5)	3/40 (8)	5/80 (6)
Injection site hemorrhage	0	2/40 (5)	2/80 (3)
Infections and infestations	4/40 (10)	3/40 (8)	7/80 (9)
Pneumonia	0	2/40 (5)	2/80 (3)
Investigations	12/40 (30)	16/40 (40)	28/80 (35)
Blood triglycerides increased	6/40 (15)	6/40 (15)	12/80 (15)
Alanine aminotransferase increased	3/40 (8)	6/40 (15)	9/80 (11)
Blood cholesterol increased	5/40 (13)	2/40 (5)	7/80 (9)
Aspartate aminotransferase increased	2/40 (5)	3/40 (8)	5/80 (6)
SpO_2 decreased	2/40 (5)	2/40 (5)	4/80 (5)
Lipase increased	1/40 (3)	2/40 (5)	3/80 (4)
Nervous system disorders	2/40 (5)	2/40 (5)	4/80 (5)
Psychiatric disorders	3/40 (8)	1/40 (3)	4/80 (5)
Respiratory, thoracic and mediastinal disorders	3/40 (8)	3/40 (8)	6/80 (8)
Vascular disorders	2/40 (5)	3/40 (8)	5/80 (6)

TEAEs are defined as any AE that started or worsened in severity on or after the first dose of study drug but no later than 28 days after the last dose of study drug. Events considered as possibly related to study drug that occur in follow-up >28 days after last study drug are also considered TEAEs. AEs are sorted by alphabetical SOC, and within SOC, by decreasing total frequency of preferred term counts. Participants are counted only once per unique SOC and once per unique preferred term within SOC. Percentages are based on the number of subjects in the analysis set by treatment group.
AE: Adverse event; SOC: System organ class; SpO_2: Oxygen saturation; TEAE: Treatment-emergent adverse event.

assumption was based on the original protocol and intended enrollment, before amending to add a discrete Part B after prespecified interim safety and efficacy analysis.

Change from baseline in viral load was compared using the TaqPath assay between the study groups using analysis of covariance with treatment as a factor and $\log_{10}$ baseline viral load as a covariate. The least squares mean change and standard error of means in each group, the differences between two groups in least squares mean change with corresponding 95% CIs, and p-values are presented. Statistical significance at day 5 was assessed using a 1-sided 0.025-level test. See additional information on this end point in the Supplementary text.

Wilcoxon–Mann–Whitney test was used for the evaluation of median days to clinical recovery with 1-sided alpha = 0.025. Participants without observed clinical recovery had a clinical recovery time of 15 days assigned to preserve the ranks for the comparison. Statistical calculations and analyses were performed using SAS/STAT v9.4 (SAS Institute Inc., NC, USA).

Efficacy analyses were performed on the intent-to-treat (ITT) population, which included all randomized participants, and the modified ITT (mITT) population, which included participants in the ITT population who had a positive SARS-CoV-2 quantitative reverse transcription PCR test result at baseline who received ≥1 dose of study drug. Safety analyses were performed on the safety population, which included all participants who received

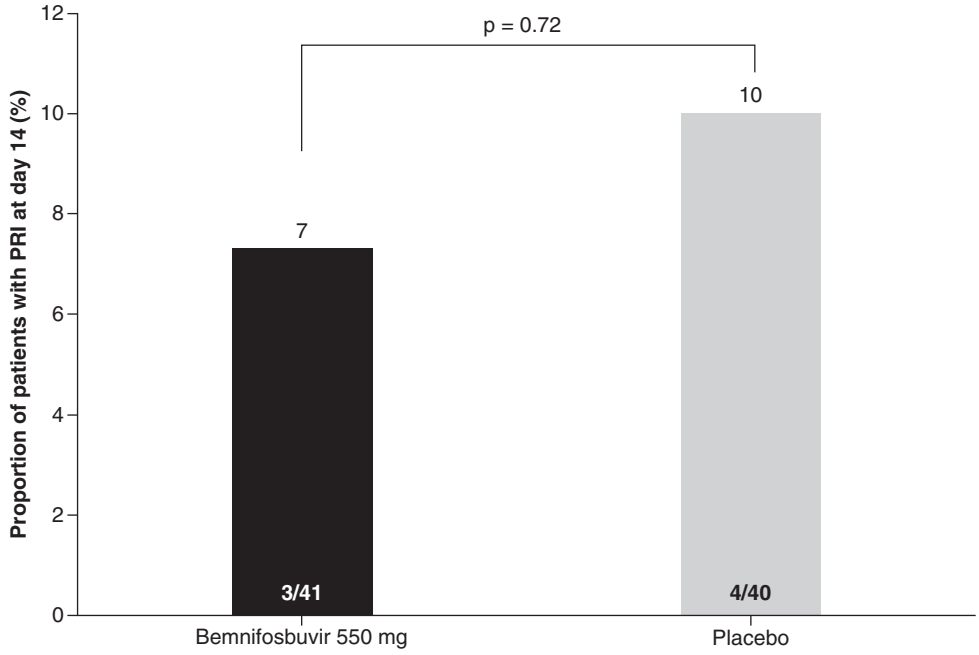

Figure 2. Progressive respiratory insufficiency at day 14.
PRI: Progressive respiratory insufficiency.

≥1 dose of study drug. A data safety board, comprising two independent clinical experts and an independent statistician, periodically assessed the safety and potential risks and benefits of this study.

Results

During this phase II study, beginning in September 2020 and ending in February 2022, 81 adult participants were randomized to Part A (bemnifosbuvir, n = 41; placebo, n = 40) in the ITT population (Figure 1). Two participants were randomized to Part B (bemnifosbuvir, n = 0; placebo, n = 2). The enrollment in Part B was limited owing to the evolving standard of care as the pandemic progressed; subjects with moderate disease were no longer being hospitalized, and those who were had alternative treatment options. Participant demographics were generally balanced across both treatment groups in Part A (Table 1).

Safety

Out of 80 evaluable participants in the safety analysis set for Part A, TEAEs were reported in 60.0% (n = 24/40) receiving bemnifosbuvir and 57.5% (n = 23/40) receiving placebo (Table 2). Most TEAEs were mild to moderate in nature and deemed unrelated to study drug. Five percent (n = 2/40) had TEAEs leading to treatment discontinuation reported with bemnifosbuvir; both participants had decreased oxygen saturation considered severe, related to progressive disease and not related to study drug by the investigator. Ten percent (n = 4/40) discontinued placebo treatment owing to TEAEs including decreased oxygen saturation, increased alanine aminotransferase, aspartate aminotransferase, blood triglycerides and transaminases. Two deaths (2/40, 5%) were reported in the placebo group in Part A and 1 (1/2, 50%) in Part B (only two participants were in this group; both received placebo).

Efficacy

The efficacy end points presented here are a subset of those initially planned as the study was discontinued. Overall, PRI was reported at day 14 in 7.3% (n = 3) of 41 participants receiving bemnifosbuvir compared with 10.0% (n = 4) of 40 participants receiving placebo (Figure 2). Because of the low enrollment numbers and the low disease progression rates, the study was insufficiently powered to determine any statistical differences between the treatment groups.

All-cause mortality was reported in three participants in the placebo group across the entire study. In Part A, all-cause mortality was reported in 0% (n = 0/41) participants receiving bemnifosbuvir versus 5% (n = 2/40) of

participants receiving placebo (n = 1, hemodynamic instability secondary to COVID-19; n = 2, COVID-19-related respiratory failure). One participant (n = 1/2) receiving placebo in Part B had a serious adverse event that resulted in death (pulmonary embolism, a COVID-19-related complication).

Of the 81 randomized participants in Part A, 71 participants were evaluable for changes in viral load from baseline. These participants had a median baseline viral load of 5.36 $\log_{10}$ copies/ml. Virology results indicated that treatment with bemnifosbuvir rapidly reduced the SARS-CoV-2 viral load from baseline, as measured by PCR of nasopharyngeal swabs. Compared with placebo, participants on bemnifosbuvir had a 0.61 $\log_{10}$ (95% CI: -1.38–0.16) greater mean reduction from baseline viral load on day 2, and this trend was sustained through day 8 (Figure 3A). The proportions of subjects in the overall study population achieving nondetectable levels of virus (TaqPath assay), as well as sustained nondetectable levels, were similar in both groups (Figure 3B).

The median time to clinical recovery, achieved by 33/41 (80.5%) participants receiving bemnifosbuvir compared with 32/40 (80.0%) participants receiving placebo, was 6 days for both groups. There were no significant differences

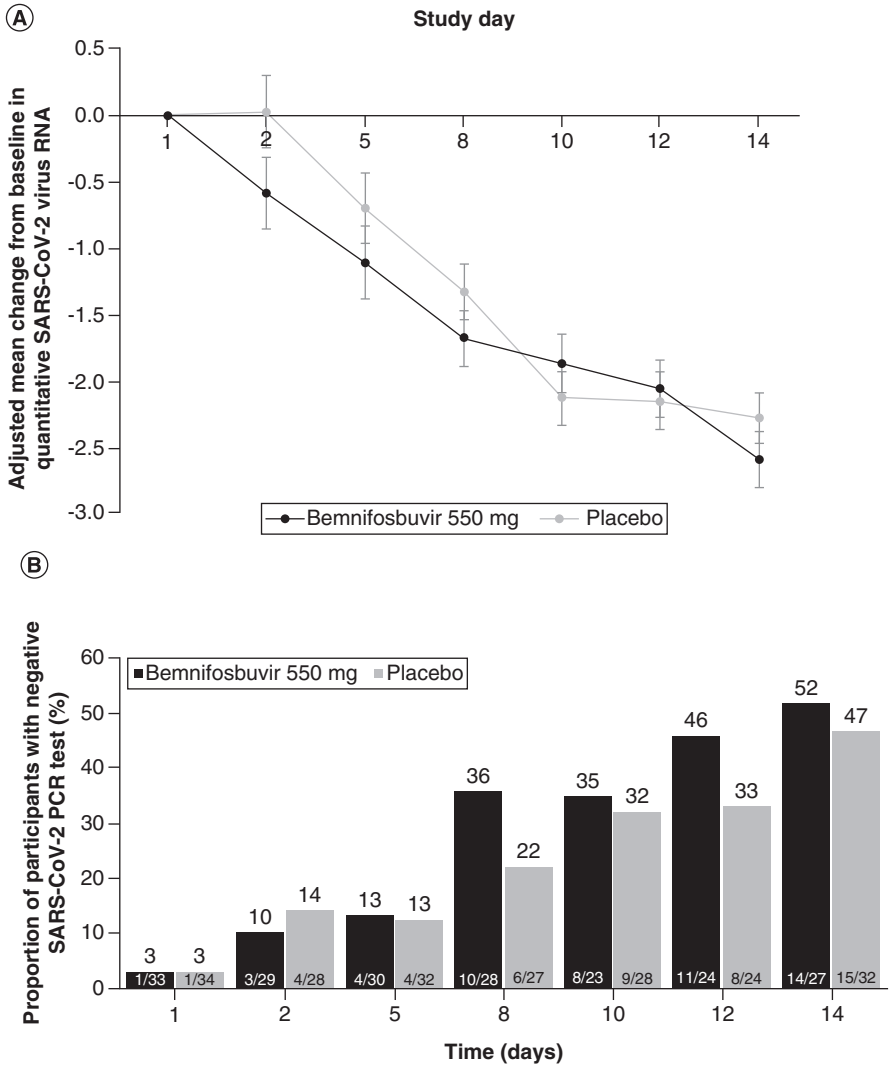

Figure 3. SARS-CoV-2 clearance. (A) ANCOVA adjusted mean change from baseline in quantitative SARS-CoV-2 virus RNA (adjusted for baseline SARS-CoV-2 RNA), modified intent-to-treat population. Error bars denote standard error (SE). **(B)** Proportion of participants with negative SARS-CoV-2 PCR test, modified intent-to-treat population. Error bars denote SE. **(C)** ANCOVA adjusted mean change from baseline in quantitative SARS-CoV-2 virus RNA (adjusted for baseline SARS-CoV-2 RNA) for participants with baseline viral load ≥5.36 $\log_{10}$. Error bars denote SE. **(D)** Proportion of participants with baseline viral load ≥5.36 $\log_{10}$ with negative SARS-CoV-2 PCR test. Error bars denote SE.

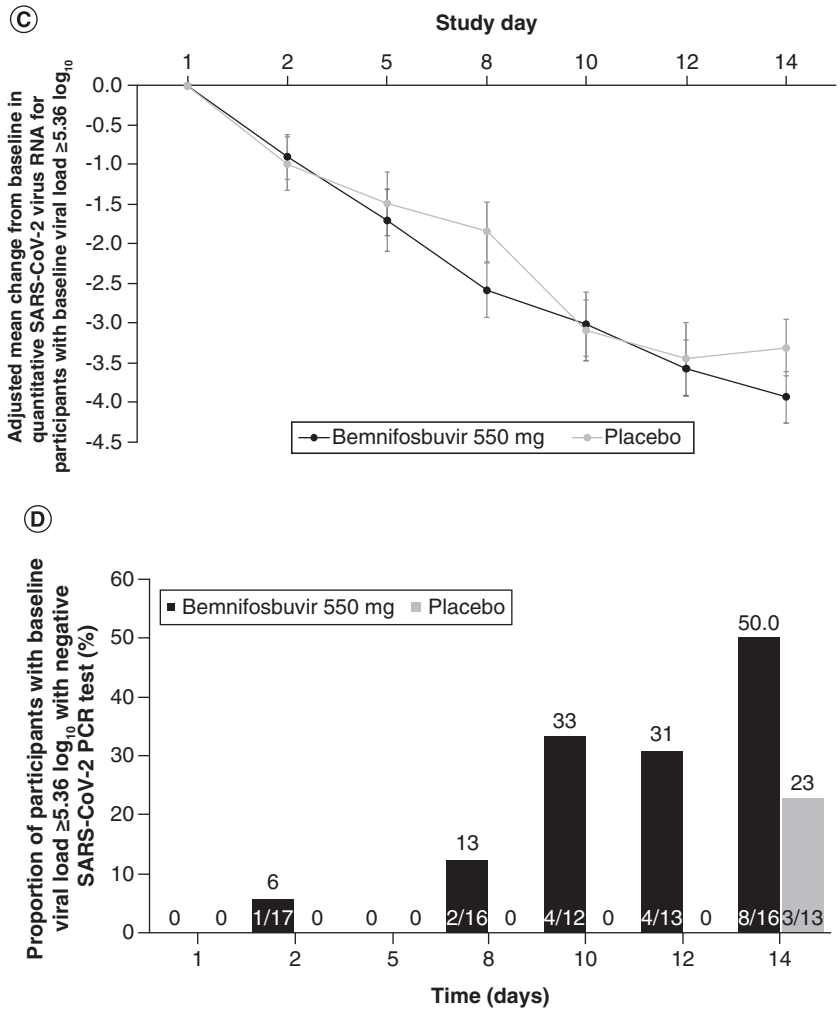

Figure 3. SARS-CoV-2 clearance (cont.). (A) ANCOVA adjusted mean change from baseline in quantitative SARS-CoV-2 virus RNA (adjusted for baseline SARS-CoV-2 RNA), modified intent-to-treat population. Error bars denote standard error (SE). **(B)** Proportion of participants with negative SARS-CoV-2 PCR test, modified intent-to-treat population. Error bars denote SE. **(C)** ANCOVA adjusted mean change from baseline in quantitative SARS-CoV-2 virus RNA (adjusted for baseline SARS-CoV-2 RNA) for participants with baseline viral load $\geq$5.36 $\log_{10}$. Error bars denote SE. **(D)** Proportion of participants with baseline viral load $\geq$5.36 $\log_{10}$ with negative SARS-CoV-2 PCR test. Error bars denote SE.

in time to resolution of symptoms (bemnifosbuvir, median 12 days [95% CI: 8.0–14.0]; placebo, median 13 days [95% CI: 9.0–21.0]).

In a *post hoc* analysis, key efficacy end points were also assessed in participants with baseline viral loads greater than or equal to the median of 5.36 $\log_{10}$ copies/ml (bemnifosbuvir, n = 18; placebo, n = 16). In these 34 participants, viral load reduction was also greater days 5 through 8 in participants receiving bemnifosbuvir compared with placebo (Figure 3C). On day 14, 50.0% (n = 8/16) of participants on bemnifosbuvir and 23.1% (n = 3/13) on placebo were PCR negative when assessed by the TaqPath assay (Figure 3D). In the bemnifosbuvir group, 12.5% (n = 2/16) participants were PCR negative as early as day 8. The difference in median time to clinical recovery was not clinically meaningful or statistically significant between treatment groups. Median time to symptom resolution was 13 days for both groups.

Discussion

The results of this phase II trial demonstrated bemnifosbuvir as safe and well tolerated at the dose of 550 mg b.i.d. for 5 consecutive days compared with placebo in participants with moderate COVID-19 who were high risk and hospitalized/in a hospital setting. Although study results are limited owing to the early termination, smaller

population and lower rates of PRI, a trend in prevention of mortality and viral load reduction was observed. Of note, the only deaths reported throughout the study were COVID-19 related, and all three occurred in the placebo group. Participants treated with bemnifosbuvir experienced more rapid reduction in viral load compared with placebo as early as day 2, which was sustained through day 8. This trend was also apparent when participants with a higher median viral load were evaluated. These preliminary results for bemnifosbuvir suggest a potential role for bemnifosbuvir in blunting disease progression in participants with moderate COVID-19 who were at high risk for poor outcomes. In an observational, retrospective study, treatment with molnupiravir or nirmatrelvir/ritonavir also resulted in faster viral load clearance in hospitalized participants, as well as lower risk for disease progression and decreased all-cause mortality [33]. Future trials, as well as real-world studies with bemnifosbuvir will be important for understanding efficacy and safety as observations made [34].

Multiple factors may have contributed to the inability of this study to meet its primary efficacy end point. Low enrollment in the study owing to early termination made it impossible to achieve the original target of 91 participants enrolled per study arm for statistical analysis. The number of PRI events was also low in both arms (bemnifosbuvir, n = 3; placebo, n = 4) owing in part to increased COVID-19 awareness throughout the duration of the study and improvements in disease management strategies. These participants also had moderate COVID-19; management shifted from hospital to home settings. Of those enrolled, a higher percentage of participants in the bemnifosbuvir arm had >1 comorbidity (42.9% vs 25.8%) compared with placebo, which may also have influenced the number of PRI events or lack of detectable differences between the two groups (Table 1).

In addition to its favorable safety profile, bemnifosbuvir exhibits antiviral activity across SARS-CoV-2 variants *in vitro* [17,21,22] and has shown low risk for interacting with other drugs [21,23–25]. Due to the continued need for viable treatment options for COVID-19 patients, the FDA granted a Fast Track designation to bemnifosbuvir in April 2023 [35]. Bemnifosbuvir is currently under investigation in a global phase III clinical trial for outpatients at high risk for disease progression (SUNRISE-3; NCT05629962) [36,37].

Conclusion

As the pandemic continues, breakthrough infections and reinfections continue to occur in vaccinated individuals [9]. Although the scientific community has made significant progress in the development of vaccines, monoclonal antibodies [10] and small molecule agents [12] to ameliorate and treat COVID-19 [11], current commonly-used antivirals are associated with concerns of rebound [13], drug–drug interactions [14], mutagenesis [15] and reproductive toxicity [16], leaving an unmet need for oral treatments for high-risk patients [11,17]. Bemnifosbuvir may address these limitations with its dual mechanism of action [20], *in vitro* data supporting efficacy toward Omicron and all related variants reported to date [17,21,22], its tolerable safety profile, oral administration and low potential for drug–drug interactions [21,23–25,36]. These qualities also provide rationale for the follow-up phase III clinical trial currently underway [37].

Summary points

- There is an unmet need for safe, oral, direct-acting, efficacious, antiviral agents with broad utility to treat infection with SARS-CoV-2.
- Progressive respiratory insufficiency was reported in 7.3% (n = 3/41) participants on bemnifosbuvir versus 10% (n = 4/40) on placebo.
- Participants receiving bemnifosbuvir had greater mean reduction in viral load from day 2 through 8.
- All-cause mortality was only reported for participants receiving placebo.
- Treatment-emergent adverse events were similar for both treatment groups and most were mild to moderate and unrelated to study drug.
- Bemnifosbuvir was found to have efficacy *in vitro* toward all variants to date, including Omicron BA.1, BA.2, BA.4, BA.5 and XBB.
- Treatments that were effective earlier in the pandemic are no longer recommended for use owing to decreased efficacy toward recent variants, and current commonly used antivirals are associated with concerns of rebound and drug–drug interactions.
- Bemnifosbuvir may address these limitations with its dual mechanism of action, *in vitro* data supporting efficacy across variants, its tolerable safety profile, oral administration and low potential for drug–drug interactions.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fvl-2023-0064

Author contributions

All authors were involved in the development of the study protocols; in the collection, analysis and interpretation of study data; in writing of the clinical study report; and in the decision to submit the article for publication.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, informed consent has been obtained from the participants involved.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data. De-identified, individual data that underlie the results reported in this article (text, tables, figures and appendices), along with the study protocol will be available indefinitely for anyone who wants access to them. The protocol and statistical analysis plan are included in the Supplementary Material.

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