

# The COVID-19 Treatment Guidelines Panel’s Statement on the Role of Bebtelovimab for the Treatment of High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19

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On February 11, 2022, the Food and Drug Administration issued an Emergency Use Authorization (EUA) for the anti-SARS-CoV-2 monoclonal antibody (mAb) bebtelovimab for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease.<sup>1</sup> Bebtelovimab is a recombinant neutralizing human mAb that binds to the spike protein of SARS-CoV-2. Based on in vitro data, bebtelovimab is expected to have activity against a broad range of SARS-CoV-2 variants, including the B.1.1.529 (Omicron) variant of concern (VOC) and its BA.1 and BA.2 subvariants.<sup>2,3</sup>

## Purpose of This Statement

The COVID-19 Treatment Guidelines Panel (the Panel) previously provided recommendations for 4 drugs with activities against the Omicron VOC (ritonavir-boosted nirmatrelvir [Paxlovid], sotrovimab, remdesivir, and molnupiravir) that can be used as treatment for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease (see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#) for more information). The purpose of this statement is to provide clinicians with guidance on the role of bebtelovimab as an additional treatment option for this patient population.

## Recommendations

### *Preferred Therapies*

For nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, the Panel recommends using 1 of the following therapies (listed in order of preference):

- **Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged  $\geq 12$  years and weighing  $\geq 40$  kg (**AIIa**).
- **Sotrovimab 500 mg** as a single intravenous (IV) infusion, administered as soon as possible and within 7 days of symptom onset in those aged  $\geq 12$  years and weighing  $\geq 40$  kg (**AIIa**).
- **Remdesivir 200 mg IV** on Day 1, followed by **remdesivir 100 mg IV** once daily on Days 2 and 3, initiated as soon as possible and within 7 days of symptom onset in those aged  $\geq 12$  years and weighing  $\geq 40$  kg (**BIIa**).

### *Alternative Therapies*

**If none of the preferred therapies for high-risk, nonhospitalized patients are available, feasible to deliver, or clinically appropriate (e.g., due to drug-drug interactions, concerns related to renal or hepatic function), the Panel recommends using 1 of the following therapies (listed in alphabetical order):**

- **Bebtelovimab 175 mg** as a single IV infusion, administered as soon as possible and within 7 days of symptom onset in those aged  $\geq 12$  years and weighing  $\geq 40$  kg, **ONLY** if none of the preferred therapies are available, feasible to deliver, or clinically appropriate (**CIII**).

- The data that support the use of this anti-SARS-CoV-2 mAb largely come from in vitro studies that demonstrated its potent activity across a broad spectrum of VOCs (including both the BA.1 and BA.2 subvariants of Omicron) and a Phase 2 randomized trial that showed no unexpected safety events and more rapid viral decay in patients at low risk for progression to severe disease.<sup>1-3</sup>
- Although there are insufficient data on hospitalization and mortality outcomes in patients at high risk of disease progression who have received bebtelovimab, the agent has a mechanism of action similar to other anti-SARS-CoV-2 mAbs that have demonstrated a reduction in hospitalization or death in high-risk patients in Phase 3 trials.
- Thus, the laboratory and Phase 2 clinical data for bebtelovimab, coupled with the aggregate evidence for this class of agents, support the use of bebtelovimab in high-risk patients when other options are not available, feasible to deliver, or clinically appropriate.
- **Molnupiravir 800 mg** orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged  $\geq 18$  years, **ONLY** if none of the preferred therapies are available, feasible to deliver, or clinically appropriate (**CIIa**).
  - Although the preferred treatment options have not been evaluated in head-to-head comparative trials, efficacy in preventing hospitalization or death was substantially less for molnupiravir in a Phase 3 trial than reported for ritonavir-boosted nirmatrelvir, sotrovimab, or remdesivir in similar efficacy trials.

## Rationale

As noted above, multiple therapeutic agents are currently available and recommended by the Panel for the treatment of nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression while Omicron is the predominant variant in the United States. The Panel favors ritonavir-boosted nirmatrelvir, sotrovimab, or remdesivir as the preferred therapies for these patients, primarily based on an 79% to 88% reduction in hospitalization or death in treated patients in randomized, placebo-controlled trials, as well as on the agents' in vitro activities against the Omicron VOC.

If **ritonavir-boosted nirmatrelvir**, **sotrovimab**, or **remdesivir** are not available, feasible to deliver, or clinically appropriate, the Panel recommends using either **bebtelovimab (CIII)** or **molnupiravir (CIIa)**. The Panel's recommendation on bebtelovimab is primarily based on laboratory data showing its potent activity against the Omicron VOC, its BA.1 and BA.2 subvariants, and other VOCs and on limited clinical trial data. The assessment of the clinical efficacy of bebtelovimab is limited to 1 small, Phase 2, randomized, placebo-controlled trial in patients at low risk of disease progression and 1 small randomized controlled trial that compared bebtelovimab to an anti-SARS-CoV-2 mAb combination of bamlanivimab, etesevimab, and bebtelovimab in patients at high risk of disease progression (described below). The MOVE-OUT trial that compared the use of molnupiravir to placebo reported a 30% reduction in rate of hospitalization or death in the molnupiravir recipients, which is markedly lower than the rate reduction reported with the use of ritonavir-boosted nirmatrelvir, sotrovimab, or remdesivir.<sup>4</sup> More detailed information regarding these therapies can be found in [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

## Additional Considerations

- Bebtelovimab is given at a dose of 175 mg as an IV infusion over  $\geq 30$  seconds. Patients should be observed for  $\geq 1$  hour after the infusion.
- Based on information from 602 participants who were exposed to bebtelovimab in clinical trials, adverse reactions due to the anti-SARS-CoV-2 mAb were rare, with infusion-related reactions,

rash, or pruritis reported in <1% of the participants.

- The risk for progression to severe COVID-19 in high-risk patients is substantially greater for those who are not vaccinated or those who are vaccinated but who are not expected to mount an adequate immune response to the vaccine due to an underlying immunocompromising condition. When logistical or supply constraints make it impossible to offer the available therapies to all eligible patients, please see [the Panel's statement on patient prioritization for outpatient therapies](#).

## Clinical Trial and Virologic Data for Bebtelovimab

The clinical data that support the EUA for bebtelovimab come from results for select arms in the Phase 2 BLAZE-4 clinical trial, which included nonhospitalized patients with mild to moderate COVID-19. Currently, there are no peer-reviewed publications on these data. The information summarized below is derived from the EUA fact sheet.<sup>1</sup> The Phase 2 clinical trial was conducted before the Omicron VOC became the predominant circulating variant.

### *Low-Risk Patients*

In treatment arms 9 through 11 of the BLAZE-4 trial, participants at low risk of disease progression were randomized 1:1:1 to receive a single infusion of a combination of 3 anti-SARS-CoV-2 mAbs (bamlanivimab, etesevimab, and bebtelovimab; n = 127), bebtelovimab alone (n = 125), or placebo (n = 128). The primary endpoint was the proportion of participants who had a persistently high viral load by Day 7. The mean duration of symptoms at enrollment was 3.6 days. The proportion of participants with persistently high viral loads was 21% in the placebo arm, 13% in the mAb combination arm ( $P = 0.098$  for comparison vs. placebo), and 14% in the bebtelovimab alone arm ( $P = 0.147$  for comparison vs. placebo). The mean decline in viral load at Day 5 was greater in the 2 arms that received anti-SARS-CoV-2 mAbs than in the placebo arm. There were few COVID-19-related hospitalizations or deaths from any cause by Day 29 across the arms. The endpoint event occurred in 3 participants (2.4%) in the combination anti-SARS-CoV-2 mAb arm, 2 participants (1.6%) in the bebtelovimab arm, and 2 participants (1.6%) in the placebo arm. The median time to sustained symptom resolution was 6 days in the bebtelovimab alone arm and 8 days in the placebo arm ( $P = 0.003$ ).

### *High-Risk Patients*

In an open-label portion of the BLAZE-4 trial (i.e., arms 12 and 13), participants at high risk of disease progression were randomized to receive either a single infusion of a combination of anti-SARS-CoV-2 mAbs (bamlanivimab, etesevimab, and bebtelovimab; n = 50) or bebtelovimab alone (n = 100). The efficacy endpoints included the proportion of participants who were hospitalized for a COVID-19-related reason or died from any cause by Day 29 and a change in viral load. The mean duration of symptoms at enrollment was 4.7 days. There was no difference between the arms in the proportion of patients who were hospitalized or who died; the endpoint event occurred in 2 participants (4%) in the combination mAb arm and 3 participants (3%), including 1 participant who died, in the bebtelovimab alone arm. The mean viral load declines in the bebtelovimab alone and combination mAb arms were comparable.

### *Virologic Activity*

Laboratory studies show that bebtelovimab at low concentrations has neutralizing activity against a broad range of SARS-CoV-2 variants, including the Omicron VOC and its BA.1 and BA.2 subvariants. In the clinical studies summarized above, which were conducted before the Omicron surge, bebtelovimab demonstrated antiviral activity.<sup>1-3</sup>

In summary, there are in vitro data showing that bebtelovimab is active against all SARS-CoV-2 variants, including the Omicron VOC and its BA.1 and BA.2 subvariants. In a Phase 2 study in

patients at low risk of disease progression who were predominantly infected with the B.1.617.2 (Delta) or B.1.1.7 (Alpha) variants, bebtelovimab demonstrated virologic activity and reduced symptom duration. However, there are limited clinical data on the use of bebtelovimab in patients with mild to moderate COVID-19 who are at high risk of disease progression (the population for which the antibody is authorized). Larger randomized controlled trials are needed to fully evaluate its efficacy in this population. Nevertheless, when other options are not available, feasible to deliver, or clinically appropriate, use of bebtelovimab is supported by the in vitro susceptibility data described above, its antiviral activity and clinical benefits seen in Phase 2 trials, and its mechanism of action, which is similar to other, authorized anti-SARS-CoV-2 mAbs that have shown definitive clinical benefit for nonhospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19.

## References

1. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for bebtelovimab. 2022. Available at: <https://www.fda.gov/media/156152/download>.
2. Westendorf K, Wang L, Zentelis S, et al. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. *bioRxiv*. 2022;Preprint. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33972947>.
3. Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 omicron sublineages. *bioRxiv*. 2022;Preprint. Available at: <https://www.biorxiv.org/content/10.1101/2022.02.07.479306v1>.
4. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med*. 2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34914868>.