

CORRESPONDENCE

Molnupiravir for Covid-19 in Nonhospitalized Patients

TO THE EDITOR: In their report on the MOVE-OUT trial, Jayk Bernal et al. (Feb. 10 issue)¹ present **improbable statistical results**. Overestimated treatment effects in interim analyses are well understood.² Much less common is a reversal of the treatment effect from the interim analysis to the next analysis. Initially, a planned interim analysis from Merck showed an efficacy of approximately 50% with respect to the primary outcome of hospitalization for any cause or death through day 29, with a primary outcome event occurring in 28 of 385 participants who received molnupiravir and in 53 of 377 participants who received placebo.^{1,3} The efficacy later decreased to approximately 30% (a primary outcome event occurred in 48 of 709 participants who received molnupiravir and in 68 of 699 participants who received placebo).¹

This difference was driven by an increased benefit with placebo in the post-interim analysis phase, with a primary outcome event occurring in 20 of 324 participants who received molnupiravir and in 15 of 322 participants who received placebo. **The disparity between these periods is so large that the difference is statistically implausible.** Furthermore, at a key Food and Drug Administration advisory meeting for emergency use authorization for molnupiravir,³ researchers from Merck presented data across 10 countries. **In the primary analysis, point estimates of absolute risk differences varied from -19.6 percentage points in Brazil to 9.1 percentage points in Guatemala, with mutually exclusive confidence intervals.**

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1. 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* 2022;386:509-20.

2. Bassler D, Briel M, Montori VM, et al. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA* 2010;303:1180-7.

3. Curtis S, Hazuda D, Blanchard K, et al. Molnupiravir. Presented at the virtual FDA Antimicrobial Drugs Advisory Committee Meeting, November 30, 2021:slide 88 (<https://www.fda.gov/media/154472/download>).

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TO THE EDITOR: In the trial conducted by Jayk Bernal et al., according to the results of the subgroup analysis of SARS-CoV-2 nucleocapsid antibody status at baseline, a benefit was observed only in the participants with negative status, among whom the adjusted risk difference was -5.1 percentage points (95% confidence interval [CI], -8.8 to -1.6); the adjusted risk difference among those with positive status was 2.3 (95% CI, -1.7 to 7.1). The data from the participants with positive status corresponds to 21% of the trial sample, which is unlikely to include participants with a reinfection given the state of the pandemic when the trial was conducted.¹ Therefore, we could hypothesize that the participants who already had antibody production at the time of diagnosis² either had received a diagnosis at a later stage of the infection than those with negative status or had an early immune response.³ The importance of early treatment was considered in investigations such as the Randomised Evaluation of Covid-19 Therapy (RECOVERY) trial.⁴ Do only persons who have not started to mount an immune response receive a benefit from treatment, or is it just a matter of time from the onset of infection? Should SARS-CoV-2 nucleocapsid antibody status be determined before starting treatment?

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1. Flacco ME, Acuti Martellucci C, Soldato G, et al. Rate of reinfections after SARS-CoV-2 primary infection in the population of an Italian province: a cohort study. *J Public Health (Oxf)* 2021 September 8 (Epub ahead of print).
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3. Guo L, Ren L, Yang S, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). *Clin Infect Dis* 2020;71:778-85.
4. RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet* 2021;397:2049-59.

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TO THE EDITOR: The most striking aspect of the trial of molnupiravir by Jayk Bernal et al. is the discrepancy between the interim results (48.2% efficacy) and the final results (29.9% efficacy). The researchers suggest that the lower estimate of the drug effect in the final results could be due to “imbalances between the analysis samples, shifts in the epidemiology of the Covid-19 pandemic, and regional variation among the enrolled participants,” and the editorialist singles out “pre-existing SARS-CoV-2 nucleocapsid antibodies and lower viral load at enrollment.”¹ However, examination of Figure S3 in the Supplementary Appendix of their article (available with the full text of the article at NEJM.org) reveals a much simpler explanation: this drug is relatively ineffective against the B.1.617.2 (delta) variant. By my calculation, the efficacy against the delta variant was 23.7%, whereas the pooled efficacy against other strains of SARS-CoV-2 was 60.2%. According to a press release from Merck, the interim data were obtained from participants who were enrolled from May through early August 2021, well before the delta variant took over as the dominant strain worldwide.² The final results, on the contrary, included data from participants who were enrolled during the era of the delta variant (August through October 2021).

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1. Whitley R. Molnupiravir — a step toward orally bioavailable therapies for Covid-19. *N Engl J Med* 2022;386:592-3.
2. Merck. Merck and Ridgeback’s investigational oral antiviral molnupiravir reduced the risk of hospitalization or death by approximately 50 percent compared to placebo for patients with mild or moderate COVID-19 in positive interim analysis of phase 3 study. October 1, 2021 (<https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderate/>).

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TO THE EDITOR: Oral medications might become an essential tool for physicians to use in the management of Covid-19 once high-quality evidence is available. This is not yet the case for molnupiravir. Jayk Bernal and colleagues claim that early treatment with molnupiravir reduces the risk of hospitalization or death among at-risk, unvaccinated adults with Covid-19. However, their results present limitations. First, the estimates are very imprecise. The absolute risk reduction with respect to hospitalization or death through day 29 varies from 0.1 to 5.9 percentage points, which corresponds to a number needed to treat ranging from 17 to 1157. Second, although vaccination coverage against Covid-19 is high in most Western countries, the efficacy of molnupiravir among vaccinated persons is unknown, and a lower baseline risk of complications might result in an even higher number needed to treat. Third, obesity (in 74% of the trial participants) was the main risk factor for severe disease in this young population (median age, 43 years). The applicability of the results in adults presenting with other risk factors, including age greater than 65 years, remains uncertain. In addition, the person-time at risk with 1433 participants was too short to establish a relevant risk–benefit balance of a drug.

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THE AUTHORS REPLY: In response to Thorlund et al.: the MOVE-OUT trial was powered to detect an overall treatment effect but not treatment–covariate interactions unless they were associated with large differences; no such differences were identified from the available data. Given the shifts in prevailing SARS-CoV-2 variants, changes in outpatient management, and inclusion of trial sites from countries with unique Covid-19 disease burdens, the trial was not necessarily conducted under uniform conditions. The differences in the results between the interim and final analyses might be statistically improbable under ideal circumstances, but they reflect the fact that several key factors could not remain constant despite a consistent trial design. We agree that there are no accepted standard methods to adjust for such situations, and therefore we prespecified unadjusted analyses for the estimation of treatment effects and absolute and relative risk reductions — all valid statistical analyses that contribute to the overall assessment of treatment benefit.

In response to Selvi-Sabater and Abellon-Ruiz: we concur that SARS-CoV-2 nucleocapsid antibody–positive status at baseline may represent either reinfection, early immune response, or delayed diagnosis. The assay we used detects total nucleocapsid antibodies but cannot distinguish different subtypes, which limits the interpretation of these data. We are currently performing additional subtype-specific (IgM or IgG) assays on positive baseline samples. However, routine baseline antibody testing is not feasible in clinical practice, because it would delay the early initiation of treatment that is so critical to successful outcomes.

In response to Levenstein: enrollment after the interim analysis indeed coincided with the emergence of the delta variant. However, multiple other factors may also have affected these results. Although a more modest treatment effect was noted among persons infected with the delta variant than among those infected with other variants, baseline sequencing for SARS-CoV-2 clade identification was incomplete at the time of our report. Multiple studies have shown preclinical

activity of molnupiravir and its active metabolite N-hydroxycytidine against SARS-CoV-2 variants of concern,^{1,3} including the delta and B.1.1.529 (omicron) variants.

In response to Roberfroid et al.: similar to the exclusions made in other trials of antiviral agents against Covid-19, vaccinated persons were excluded in the MOVE-OUT trial. The mechanism of molnupiravir is independent of the spike protein, and thus activity should not be affected by previous vaccination, which could have limited durability or decreased effectiveness with the emergence of novel variants. The direction of the estimated treatment effect in the MOVE-OUT trial favored molnupiravir over placebo with respect to all risk factors, including age greater than 60 years, except diabetes mellitus. Preclinical data, along with the clinical efficacy and safety results, suggest a favorable benefit–risk profile of molnupiravir in the treatment of Covid-19 in high-risk persons,^{4,5} particularly in consideration of the limited options that are available globally.

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Since publication of their article, the authors report no further conflict of interest.

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