Correspondence: *Dr George N. Okoli; Email: George.Okoli@umanitoba.ca*

GEORGE & FAY YEE
Centre for Healthcare Innovation

Molnupiravir for Treatment of Non-Hospitalised Adults with Laboratory-Confirmed, Mild/Moderately Severe COVID-19

A Systematic Evidence Review with Meta-Analysis and Trial Sequential Analysis

George N. Okoli • Nicole Askin • Rasheda Rabbani | University of Manitoba, Winnipeg, Manitoba, Canada

The authors declare that they have no perceived conflicts of interest

Background

Efficacy and safety of antiviral drugs for treatment of the coronavirus disease 2019 (COVID-19) remain unclear. One of the approved antiviral drugs, molnupiravir is a nucleoside analogue, which inhibits viral replication of the coronavirus strain that causes COVID-19, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by introducing errors into the viral genome. The evidence for efficacy of this antiviral drug in humans has been conflicting, raising questions about its approval for COVID-19. In view of many gaps in knowledge and accumulating evidence, we summarised published evidence on the approved molnupiravir regimen (800mg twice daily over 5 days) for treatment of non-hospitalised adults with mild/moderately severe COVID-19.

Methods

We systematically searched and included randomised controlled trials (RCTs) of molnupiravir for treatment of laboratory-confirmed mild/moderately severe COVID-19 (PROSPERO registration: CRD42020216817). We conducted pooled analysis of appropriate data using an inverse variance, random-effects model, presenting relative risk (RR) with associated 95% confidence intervals. Statistical heterogeneity was calculated using the I^2 statistic. We assessed for risk of bias in the included RCTs and graded and conducted trial sequential analysis (TSA) of the evidence, a unique cumulative meta-analysis that provides information on adequacy of the overall sample size of pooled estimates to inform evidence-based clinical practice and to guide future evidence reviews on the topic.

Results

Nine RCTs (30,971 persons) made the eligibility for inclusion. Most of the trials (78%) were of a low risk of bias. There was little evidence to suggest more viral clearance for molnupiravir compared with no treatment/placebo (RR 1.08 [1.01 – 1.16], I^2 40.8%, 5 RCTs, 1,785 persons; moderate quality evidence). Molnupiravir did not reduce the risk of hospitalisation (RR 0.73 [0.47 – 1.14], I^2 58.3%, 5 RCTs, 28,626 persons; high quality evidence) and all-cause mortality (RR 0.51 [0.15 – 1.69], I^2 36.8%, 4 RCTs, 27,445 persons; high quality evidence), and was not associated with significantly more adverse (RR 1.02 [0.90 – 1.14], I^2 16.3%, 7 RCTs, 3,368 persons; moderate quality evidence) or serious adverse (RR 0.91 [0.71 – 1.16], I^2 0%, 5 RCTs, 27,562 persons; high quality evidence) events. However, TSA suggested that further RCTs are required before any conclusions can be reached regarding viral clearance **(Figure 1)**, all-cause mortality **(Figure 2)**, and adverse events **(Figure 3)**, but that further RCTs on the risk of hospitalisation **(Figure 4)**, and serious adverse events **(Figure 5)** may be futile, as the efficacy/safety of molnupiravir for these outcomes is unlikely.

Figure 1: *TSA for viral clearance*

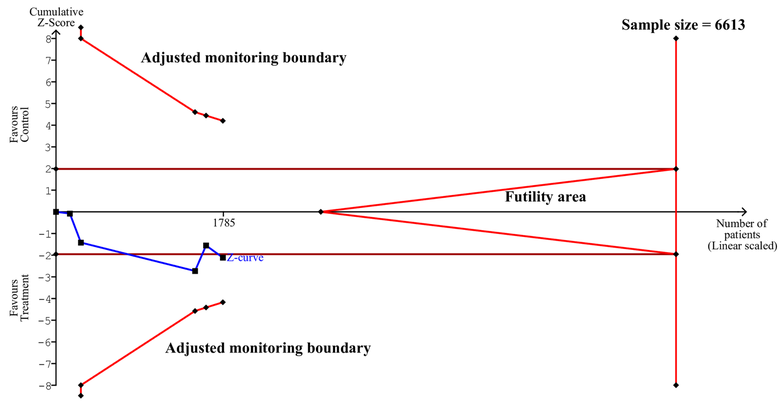


Figure 2: *TSA for all-cause mortality*

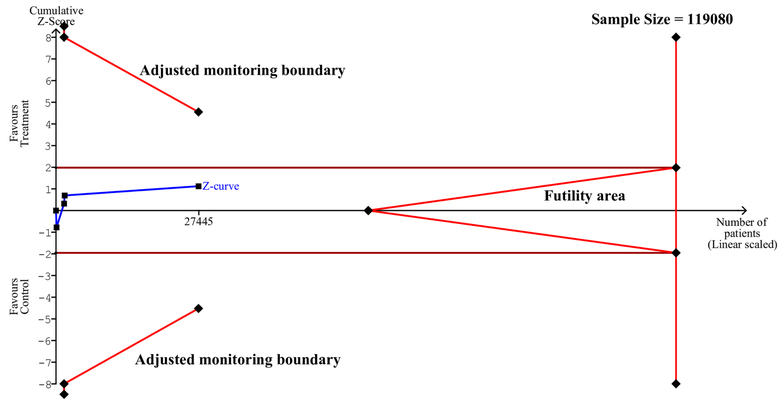


Figure 3: *TSA for adverse events*

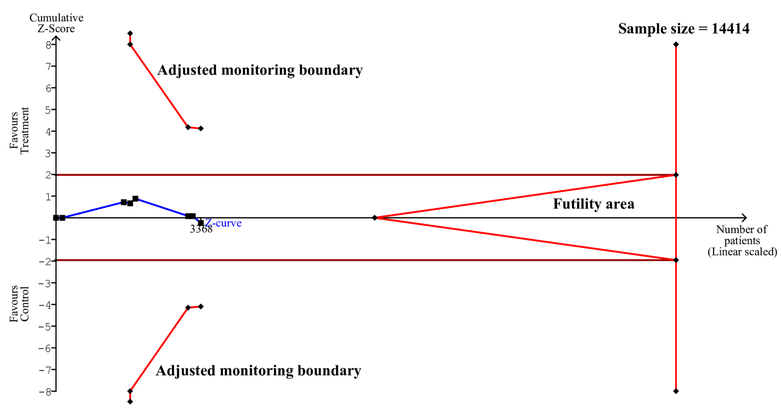


Figure 4: *TSA for hospitalisation*

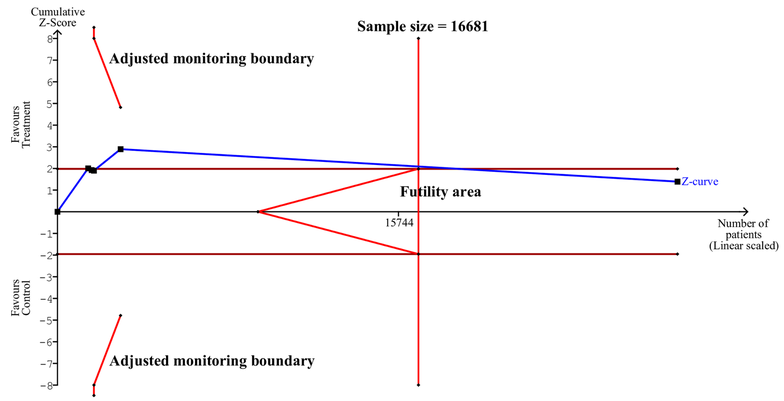
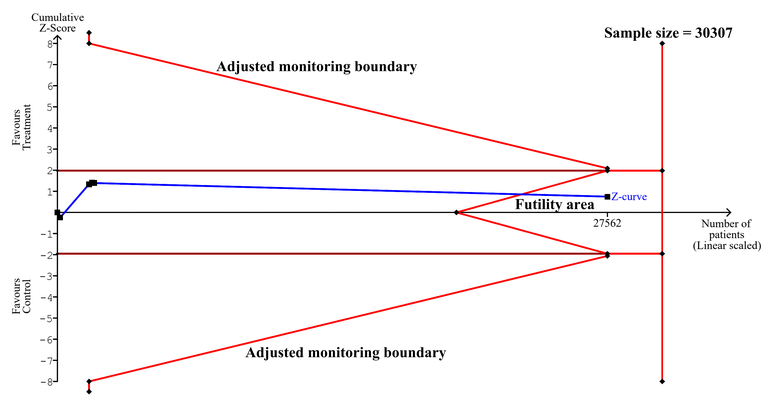


Figure 5: *TSA for serious adverse events*



Conclusions

The approved molnupiravir regimen for treatment of non-hospitalised adults with mild/moderately severe COVID-19 may be promising for clearance of the SARS-CoV-2 viral infection, but not for reducing hospitalisation or all-cause mortality although the evidence is limited and more RCTs are needed for a stronger evidence base before firm conclusions could be drawn.

References for the included studies

1. Arribas et al. NEJM Evidence. 2022;1(2).
2. Butler et al. Lancet. 2023;401(10373):281-293.
3. Caraco et al. NEJM Evidence. 2022;1(2).
4. Fischer et al. Sci Transl Med. 2022;14(628).
5. Jayk Bernal et al. N Engl J Med. 2022;386(6):509-520.
6. Johnson et al. Ann Intern Med. 2022;175(8):1126-1134.
7. Khoo et al. Lancet Infect Dis. 2023;23(2):183-195.
8. Sinha et al. Cureus. 2022;14(11): e31508.
9. Zou et al. Front Pharmacol. 2022; 13:939573.

Strategy for Patient-Oriented Research SPOR Putting Patients First
Shared health Soins communs Manitoba
University of Manitoba
Manitoba