Molnupiravir

Section last reviewed and updated 2/23/2023

Last literature search conducted 1/31/2023

Recommendation 1: In ambulatory patients (≥18 years) with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests molnupiravir initiated within five days of symptom onset rather than no molnupiravir. (Conditional recommendation†, Low certainty of evidence)

**Other options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.*

Remarks:

- Patients who will most likely benefit from antivirals are those with risk factors for progression to severe disease (e.g., elderly, those with high-risk comorbidities, incomplete vaccination status, or immunocompromised). Those without risk factors are less likely to benefit.
- Patients who put a higher value on the putative mutagenesis, adverse events, or reproductive concerns and a lower value on the uncertain benefits would reasonably decline molnupiravir.
- Patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive molnupiravir.
- Molnupiravir is not authorized under the FDA EUA for use in patients <18 years because it may affect bone and cartilage growth.
- Molnupiravir is not recommended under the FDA EUA for use during pregnancy.

- Molnupiravir is not authorized under the FDA EUA for pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19 because benefit of treatment has not been observed in individuals when treatment is started after hospitalization due to COVID-19.

†*The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.*

Figure 1. FDA EUA criteria for the use of molnupiravir [1]

Molnupiravir may only be used for the treatment of mild-to-moderate COVID-19 in adults who are at high-risk for progression to severe COVID, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Patients And Caregivers: Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019 (COVID-19). Available at: https://www.fda.gov/media/155055/download. Accessed 13 February 2023.

Why is molnupiravir considered for treatment?

Molnupiravir is an oral antiviral that targets the genetic machinery that is responsible for SARS COV-2 replication. Molnupiravir is an oral pro-drug that is converted to β-D-N4-hydroxycytidine, which acts as a substrate for RNA-dependent RNA polymerase. After it is incorporated into the viral RNA, serial mutations develop, resulting in a virus that is less fit for ongoing viral replication. One phase I RCT evaluated the safety and tolerability of molnupiravir in healthy adults without COVID-19 [1]. The study reported molnupiravir to be well tolerated, with no increased reports of serious adverse events among persons in the molnupiravir arm compared to those receiving placebo. The FDA granted EUA to molnupiravir on December 23, 2021, for the treatment of mild-to-moderate COVID-19 in adults (≥18 years) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Summary of the evidence

Five RCTs informed the recommendation for molnupiravir [2-6]. Three RCTs reported on treatment of at least partially vaccinated participants with COVID-19 with either 800 mg of molnupiravir or placebo on outcomes of mortality, hospitalization, and serious adverse events [3, 4, 6]. In the largest trial (N=26,411), PAMORAMIC, 99% of participants had at least one COVID-19 vaccine dose with 92%-93% having received three doses [3]. Two RCTs reported on treatment of unvaccinated patients with COVID-19 with either 800 mg of molnupiravir or placebo for five days [2, 5]. In one phase III trial (MOVe-OUT trial) reporting on the outcomes of death, hospitalization and serious adverse events, patients with mild-to-moderate COVID-19 received either molnupiravir or placebo within five days after the onset of symptoms. In the phase IIa trial reporting on the outcomes of death and serious adverse events in patients with symptom duration <7 days received molnupiravir or placebo.

Benefits

COVID-19-related mortality may be lower in patients receiving molnupiravir rather than placebo (RR: 0.28; 95% CI: 0.09, 0.86; low CoE); however, given the small baseline risk of mortality across the available evidence, the reduction in mortality may not be clinically meaningful (Absolute effect: 1 fewer per 1,000 persons; 95% CI: from 1 fewer to 0 fewer). COVID-19-related hospitalizations and the composite of all-cause hospitalization or death likely results in little to no difference among patients receiving molnupiravir rather than no molnupiravir (RR: 1.03; 95% CI: 0.78, 1.35; moderate CoE and RR: 0.92; 95% CI: 0.74, 1. 14; moderate CoE, respectively).

Harms

Patients treated with molnupiravir may not experience greater serious adverse events or adverse events than those receiving placebo (RR: 0.57; 95% CI: 0.22, 1.52; moderate CoE and RR: 0.81; 95% CI: 0.47, 1.40; moderate CoE, respectively).

Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals [7]. Other concerns with molnupiravir include the

possibility of viral mutagenesis in persons with compromised immune systems who are unable to clear the virus. Females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for four days after the last dose. Breastfeeding is not recommended during treatment with molnupiravir. Lactating individuals may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for four days after last dose of molnupiravir [8]. Men of reproductive potential who are sexually active with females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for at least three months after the last dose of molnupiravir. It is also not recommended in children <18 years of age for the concern of bone growth.

Molnupiravir does not require renal or hepatic dose adjustment.

Other considerations

The panel agreed that the overall certainty of evidence for treatment of ambulatory patients was low, given concerns with imprecision, driven by few reported events and a relatively small effect.

The use of molnupiravir presents additional considerations and potential concerns regarding viral mutagenesis in immunocompromised persons and safety in persons of reproductive age, for which more data are needed to quantify such effects. The panel recognized that alternative treatment options exist with the possibility of greater benefit with a smaller known safety profile. The FDA required the manufacturers to conduct additional animal studies on the impact of the drug on spermatogenesis and to establish a pregnancy registry if the drug was inadvertently administered during pregnancy.

The evidence confirms that using molnupiravir early in the disease process when viral loads are high confers maximum benefit. It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.

More recent studies in mild-to-moderate COVID-19 have shown lower rates of progression to hospitalizations or death, which could likely be due to changes in population immunity and lower virulence of recent circulating variants. Given this observation, the panel discussed about the role of patient centered outcomes (e.g., meaningful decrease in severity or duration of symptoms) other than mortality and hospitalizations in trials evaluating treatment of mild to moderate COVID-19. The panel agreed that such outcomes should be evaluated in double-blind placebo-controlled trials to reduce the risk of bias. Such outcomes also should be measured using validated instruments and should be coupled with measures of disability or quality of life. The studies evaluating molnupiravir which reported such outcomes had a high risk of bias so were not considered for making the recommendation.

Conclusions

The guideline panel suggests the use of molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who are within five days of symptom onset and have no other treatment options. More data are needed on the potential adverse effects of this medication. The evidence supporting this recommendation will be reassessed with the release of updated published information from newer trials.

Table 1. GRADE evidence profile, Recommendation 1

Question: Molnupiravir compared to no molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease

Last reviewed and updated 2/8/2023

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	molnupiravir	no molnupiravir	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow-up: range 28 days to 29 days)												
3 [1-3]	randomized trials	not serious	not serious	serious [a,b]	serious [c]	none	4/13328 (0.0%)	14/13314 (0.1%)	**RR 0.28** (0.09 to 0.86)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Hospitalizations (follow-up: 29 days)												
2 [2,3]	randomized trials	not serious	not serious	serious [b,d]	not serious	none	103/12619 (0.8%)	100/12615 (0.8%)	**RR 1.03** (0.78 to 1.35)	**0 fewer per 1,000** (from 2 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalization or death (all-cause) (follow-up: 29 days)												
2 [1,2]	randomized trials	not serious	not serious	serious [e]	not serious	none	153/13238 (1.2%)	166/13224 (1.3%)	**RR 0.92** (0.74 to 1.14)	**1 fewer per 1,000** (from 3 fewer to 2 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow-up: range 28 days to 29 days)												
5 [1-5]	randomized trials	not serious	not serious	not serious [b]	serious [c,f]	none	57/13706 (0.4%)	67/13827 (0.5%)	**RR 0.57** (0.22 to 1.52)	**2 fewer per 1,000** (from 4 fewer to 3 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse events												
4 [1,3-5]	randomized trials	not serious	not serious	not serious [b]	serious [c,f]	none	97/932 (10.4%)	106/884 (12.0%)	**RR 0.81** (0.47 to 1.40)	**23 fewer per 1,000** (from 64 fewer to 48 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Risk of bias: Study limitations **Inconsistency:** Unexplained heterogeneity across study findings **Indirectness:** Applicability or generalizability to the research question **Imprecision:** The confidence in the estimate of an effect to support a particular decision **Publication bias:** Selective publication of studies

NB: Certainty ratings are derived from evidence that has not been peer reviewed or published.

CI: Confidence interval; **HR:** Hazard ratio; **RR:** Risk ratio

Explanations

a. In Bernal 2021, after day 29, one additional death resulting from adverse events occurred in the molnupiravir group and three additional deaths occurred in the placebo group.
b. Participants included in recent large trials may not represent the population at high risk for developing severe disease.
c. Small number of events.
d. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.
e. All 10 patients reported as died at day 29 had been hospitalized.
f. 95% CI cannot exclude the possibility of harms.

References

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 **2021**: Available at: https://doi.org/10.1056/nejmoa2116044 [Epub ahead of print 16 December 2021].
2. Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. Lancet **2023**; 401(10373): 281-93.
3. Khoo SH, FitzGerald R, Saunders G, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Infect Dis **2023**; 23(2): 183-95.
4. Fischer WA, 2nd, Eron JJ, Jr., Holman W, et al. A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med **2021**: eabl7430. Available at: https://doi.org/10.1126/scitranslmed.abl7430 [Epub ahead of print 23 December 2021].
5. Zou R, Peng L, Shu D, et al. Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial. Front Pharmacol **2022**; 13: 939573.

References

1. Painter WP, Holman W, Bush JA, et al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. Antimicrob Agents Chemother **2021**; 65(5): e02428-20.
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7. U.S. Food and Drug Administration. Fact Sheet for Patients And Caregivers: Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019 (COVID-19). Available at: https://www.fda.gov/media/155055/download. Accessed 3 November 2022.
8. U.S. Food and Drug Administration. Frequently Asked Questions on the Emergency Use Authorization for Lagevrio (molnupiravir) for Treatment of COVID-19 Available at: https://www.fda.gov/media/155056/download. Accessed 13 February 2023.

Supplementary Materials

Molnupiravir

Table s1. Should ambulatory patients with mild to moderate COVID-19 at high risk for progression to sever disease receive molnupiravir vs. no molnupiravir?

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Butler 2023 [2]	UK	RCT	25783 (12821/12962)	58.6	Mean (range): 56.6 (18 to 99)	Adults with comorbidities had ongoing symptoms from COVID-19 that had started within the previous five days and a positive polymerase chain reaction (PCR) or rapid antigen SARS-CoV-2 test within the past seven days	Molnupiravir 800mg twice daily for 5 days	Usual care	Usual care	All-cause, non-elective hospital admission and/or death within 28 days of randomization Time to self-reported recovery Time to early sustained recovery (recovered by day 14 and remained recovered until day 28) Time to sustained recovery (date participant first Reported recovery and subsequently remained well until 28 days)	NIHR

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										Rating from 0-10 of how well participants felt Time to initial alleviation of symptoms (date symptoms first reported as minor or none) Time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remained minor or none until 28 days) Time to initial reduction of severity of symptoms Contacts with health and social services Hospital assessment without admission Oxygen administration	

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										New household COVID-19 infections Safety outcome measures	
Fisher 2021 [4]	10 sites in US	RCT	202	51.5	Age: Median (range by treatment arm) Molnupiravir 200 mg: 32 (19-65) Molnupiravir 400 mg: 42.5 (19-82) Molnupiravir 800 mg: 42 (18-68) Placebo: 39 (19-71)	Unvaccinated adults if they had a positive test for SARS-CoV-2 infection within 96 hours and had onset of symptoms within 7 days of treatment initiation	Molnupiravir 200 mg every 12 hours x 5 days Molnupiravir 400 mg every 12 hours x 5 days Molnupiravir 800 mg every 12 hours day x 5 days	Placebo	None	Mortality Change in SARS-CoV-2 viral load from baseline Median time to COVID-19 symptom resolution Isolation of infectious virus SAEs	Merck and Ridgeback Biotherapeutics
Jayk 2021 [1]	107 sites in 20 countries	RCT	1433 (716/717)	51.3	43.0 (Range: 18-90)	Ambulatory adults with mild or moderate COVID-19 (at least 1 symptom) with a positive SARS-CoV-2 test within 5 days and at least one risk	Molnupiravir 800 mg twice daily for 5 days	Placebo	Standard of care including: antipyretics, anti-inflammatory agents, glucocorticoids)	Mortality Hospitalization Rate of hospitalization Clinical improvement	Merck

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						factor for the development of severe disease				Serious adverse events	
Khoo 2023 [3]	UK	RCT	180 (90/90)	57.0	Median: 43	Adult out-patients (50/50 vaccinated) with PCR-confirmed SARS-CoV-2 infection within five days of symptom onset	Molnupiravir at 800mg twice daily for 10 doses over 5 days	Matching placebo twice daily for 10 doses over 5 days	Standard of care (symptomatic relief including antipyretics)	Time from randomization to negative PCR with an exploratory virological endpoint of change in viral titer Change in viral titer at day 5 Clinical progression: WHO Clinical Progression Scale for COVID- 19, NEWS2 score (UK Royal College of Physicians measuring acute illness, the FLU-PRO Patient reported outcome measures: presence and severity of influenza-like symptoms across 6 domains of	Ridgeback Biotherapeutics, UK National Institute for Health and Care Research, Medical Research Council and The Wellcome Trust

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										nose, throat, eyes, chest/respiratory, gastrointestinal and body/system at day 15 and 29 Overall survival (time-to-event) Safety and tolerability	
Zou 2022 [5]	China/Third People's Hospital of Shenzhen	RCT	108 (77/31)	44.4	Median (range) molnupiravir: 39 (20, 63) Median (range) Control: 42 (22, 61)	Adults with mild/moderate COVID-19 who tested positive for SARS-CoV-2 Omicron variant and had initial onset of symptoms for ≤5 days prior to the day of treatment	Molnupiravir (800 mg twice per day) plus basic treatment for 5 days	Basic treatment for 5 days	Basic treatment, which consisted of vitamin C, lianhuaqingwen granule, and nasal irrigation	Time of viral RNA Percentage of patients who were negative for SARS-CoV-2 infectious virus on days 5, 7, and 10 Duration of fever, time of symptom alleviation and laboratory test results (AST, ALT, CK, CK-MB, LDH, IL-6, CRP, Bun, Cr) Serious adverse events	National Key Research and Development Project, Shenzhen Science and Technology Research and Development Project and in part from the National Science and Technology Major Projects

Figure s1a. Forest plot for the outcome of mortality for molnupiravir vs. no molnupiravir

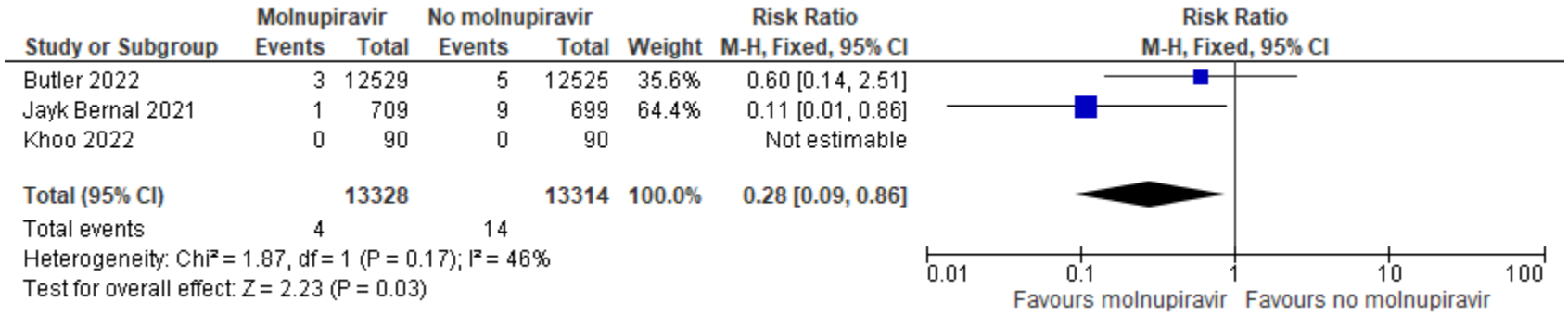

Figure s1b. Forest plot for the outcome of hospitalization for molnupiravir vs. no molnupiravir

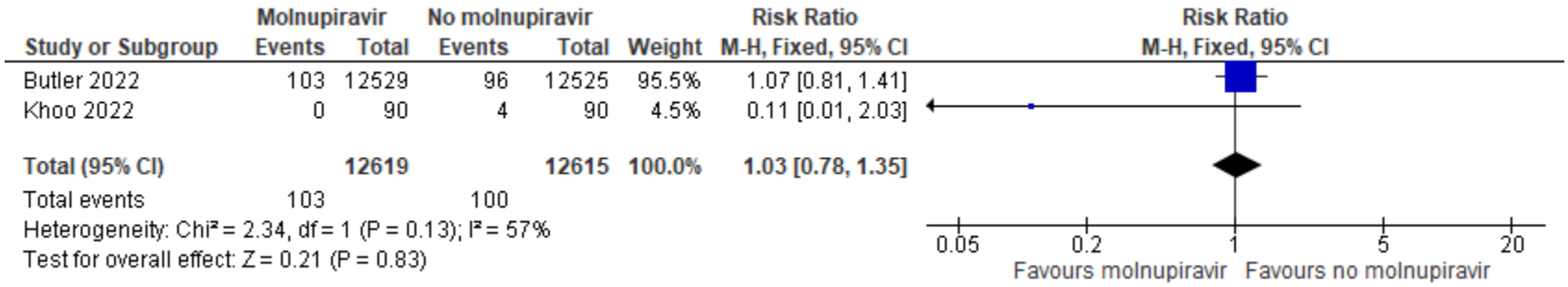

Figure s1c. Forest plot for the outcome of hospitalization or death for molnupiravir vs. no molnupiravir

Figure s1d. Forest plot for the outcome of serious adverse events for molnupiravir vs. no molnupiravir

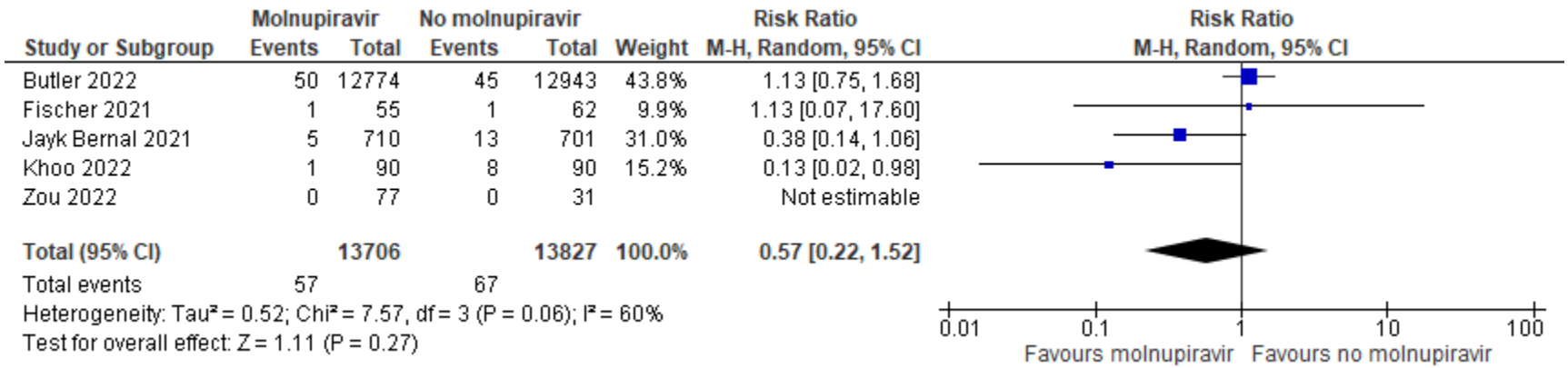

Figure s1e. Forest plot for the outcome of adverse events for molnupiravir vs. no molnupiravir

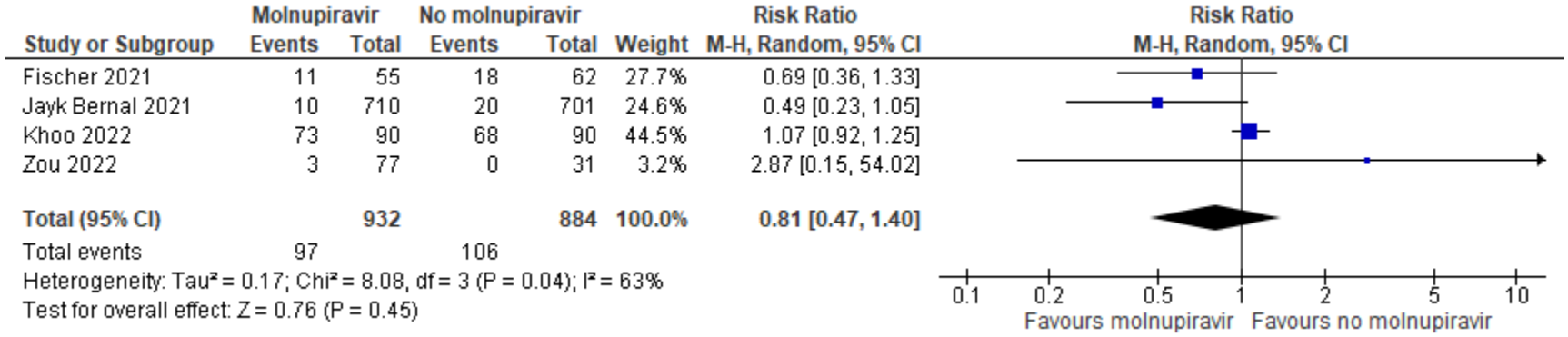

Table s2. Risk of bias for randomized controlled studies (molnupiravir vs. no molnupiravir)

Cochrane 2.0

Study	Bias in randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of outcome	Bias in selection of the reported result
Butler 2023 [2]					
Fischer 2021 [4]					
Jayk 2021 [1]					
Khoo 2023 [3]					
Zou 2022 [5]					

Low	High	Some concerns

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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 **2021**: Available at: https://doi.org/10.1056/nejmoa2116044 [Epub ahead of print 16 December 2021].
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