Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Among COVID-19 patients, should molnupiravir be used for treatment?

Updated by: Katherine Ruth O. Relato, MD, Natasha Ann R. Esteban-Ipac, MD, Marissa M. Alejandria, MD, MSc

Initial Reviewer by: Daniel Y. Guevara, MD, Carol Stephanie C. Tan-Lim, MD, MSc (Clinical Epidemiology), Natasha Ann R. Esteban-Ipac, MD

RECOMMENDATION

We suggest the use of molnupiravir within 5 days of symptom onset among non-hospitalized adult patients (18 years old and older) with mild to moderate COVID-19 infection with at least one risk factor* for progression. *(Low certainty of evidence, Weak recommendation)*

*Risk factors for progression include:
age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions or diabetes mellitus

PREVIOUS RECOMMENDATION

We suggest the use of molnupiravir within 5 days of symptom onset among non-hospitalized patients with mild to moderate COVID-19 infection with at least one risk factor* for progression. *(Low certainty of evidence, Weak recommendation)*

*Risk factors for progression include:
age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions or diabetes mellitus

Previous Consensus Issues
Molnupiravir showed general net benefit, specifically for mortality. The drug should be given specifically within the given time period (within 5 days of symptom onset). There are still issues to consider about the availability and use since it is still limited (currently available under compassionate special permit issued by FDA).

What's new in this version?

Three (3) new published RCTs (Bernal 2021, Arribas 2021 and Fischer 2021) are included in this update. One (1) study is a published version of the previously included preprint (Fischer 2021).

Key Findings

Five (5) randomized controlled trials (RCTs) studied the effect of molnupiravir on the treatment of COVID-19 compared to standard of care and/or placebo. Molnupiravir significantly decreased the need for hospitalization at day 29. Subgroup analysis based on the severity showed significant reduction in mortality in non-hospitalized mild to moderate patients but did not show significant

benefit among hospitalized mild to severe patients. For other critical outcomes, molnupiravir had no apparent effect on clinical improvement based on patient reported outcome measures (FLU-PRO), WHO COVID-19 ordinal scale, National Early Warning Score (NEWS2) and sustained recovery. Adverse events and serious adverse events were similar between molnupiravir and standard of care and/or placebo.

The phase 2a study had randomization issues and reporting bias. The serious risk of bias and imprecision led to the downgrading of evidence to low certainty.

Introduction

Molnupiravir is a small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC), which has activity against SARS-CoV-2 and other RNA viruses (coronaviruses, influenza virus, and encephalitic alphaviruses) in preclinical and in-vitro studies.[1,2]

After oral administration of molnupiravir, NHC circulates systemically and is phosphorylated intracellularly to NHC triphosphate. NHC triphosphate is incorporated into viral RNA by viral RNA polymerase and subsequently misdirects the viral polymerase to incorporate either guanosine or adenosine during viral replication. This leads to an accumulation of deleterious errors throughout the viral genome rendering the virus noninfectious and unable to replicate.

Consequently, molnupiravir was considered as a potential prophylactic and treatment agent against COVID-19 [1] and is considered safe and well-tolerated [3]

Review Methods

Pubmed, Cochrane Library, and Google Scholar were systematically searched using free text and MeSH terms for coronavirus infections, novel coronavirus, COVID-19, SARS-CoV-2, and molnupiravir. Preprints were sought in the following databases: medrxiv, biorxiv, and chinarxiv. Ongoing studies were also searched in *clinicaltrials.gov*, EU Clinical Trials Register, Cochrane COVID-19 study register, and other trial registries. The COVID-NMA Initiative was also searched. Any relevant cited references were manually searched

All RCTs that compared molnupiravir to standard of care or placebo in treating patients with confirmed COVID-19 infection were included. Eligible studies had at least one of the following outcomes: mortality, clinical deterioration, development of ARDS, need for mechanical ventilation (or ECMO), need for hospitalization, need for ICU admission, ICU/hospital length of stay, time to clinical improvement/recovery, radiographic improvement, virologic clearance by RT-PCR test, and adverse effects. For this review, no limits were placed on disease severity and age. Subgroup analysis by dose, disease severity, oxygen requirement, and age was planned. In order to compute for confidence intervals, we imputed 1 if a study had no event in the treatment arm.

Results

Characteristics of included studies

Five (5) published randomized controlled clinical trials (RCTs) (N = 1,835) investigated the effectiveness of molnupiravir among confirmed COVID-19 patients compared to placebo and/or standard of care.

Appendix 2 summarizes the characteristics of the included studies. One study is a phase 1 open-label RCT done in the UK [4], one study is a phase 2a RCT done in the US [5], three of the studies are multinational, one is a Phase2/3 trial done in 14 countries [6], one is a Phase 2/3 trial done in

15 countries [7] and one study is a Phase 3 trial done in 20 countries (Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Italy, Japan, Mexico, Philippines, Russian Federation, South Africa, Spain, Taiwan, UK, Ukraine and USA).[7] Study participants in four trials were non-hospitalized mild to moderate COVID-19 patients. [4,5,6,8]. While one study included mild to severe hospitalized patients [7]. Two of the trials included at least one risk factor for development of severe disease (age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions, diabetes mellitus or sickle cell disease).[6,8] Two studies included symptom onset within 5 days of randomization [4,8], while two studies included symptom onset within 7 days [5,6] and one study included symptom onset within 10 days [7]. One study compared molnupiravir given twice daily at 300mg, 600mg, and 800mg for 5 days to standard of care [4]. Three studies compared molnupiravir given twice daily at 200mg, 400mg, and 800mg for 5 days to placebo.[5-7] One study compared molnupiravir given 800mg twice daily for 5 days to placebo.[8] Only the results of molnupiravir given 800mg twice daily for 5 days in the phase 1 [4], phase 2a [5], phase 2/3 [6,7] studies compared to standard of care and/or placebo were pooled with the results of the Phase 3 study.[6] All of the studies administered molnupiravir orally or via nasogastric tube.

Overall Certainty of Evidence

The overall certainty of evidence was rated low due to serious risk of bias and serious imprecision on two of the critical outcomes (all-cause mortality and serious adverse events). The serious risk of bias was due to issues with randomization (imbalance in baseline characteristics of the treatment groups) in the Phase 2a study.[5] The molnupiravir group had a higher baseline prevalence of SARS-CoV-2 antibodies (30-35.3% vs. 18.2% in placebo).[5] Subgroup analysis on seronegative patients was done on the outcomes of isolation of infectious virus and time to viral RNA clearance.[5] However, it was unclear if the subgroup analysis was pre-planned. The risk of bias table is in Appendix 4. The GRADE Evidence profile is detailed in Appendix 5.

Critical outcomes

Molnupiravir showed no significant benefit in the all-cause mortality at day 29 (RR 0.51 95% CI 0.21, 1.25; I^2=48%; 4 RCTs, 1,822 participants) compared to standard of care and placebo. However, subgroup analysis on mortality based on severity showed significant benefit of molnupiravir on out-patient, mild to moderate diseases at day 29 (RR 0.23 95% CI 0.07, 0.81; I^2=0%; 3 RCTs, 1,675 participants) and no significant benefit on hospitalized, mild to severe diseases at day 29 (RR 4.35 95% CI 0.47, 39.92; 1 RCT, 147 participants).

Moreover, molnupiravir show significant reduction in the need for hospitalization at day 29 (RR 0.70 95% CI 0.50, 0.99; I^2=0%; 3 RCTs, 1,675 participants) compared to standard of care and placebo. Molnupiravir did not show significant benefit in clinical improvement by WHO COVID-19 ordinal scale (RR 0.98 95% CI 0.87, 1.10) in 1 study with 1,408 participants [8],by oxygen saturation levels (molnupiravir 800mg median 99%, range 96-100; vs. placebo median 97.5%, range 97-98), WHO COVID-19 ordinal scale (molnupiravir 800mg median 1, range 1-2; vs. placebo median 1, range 1-2), FLU-PRO (molnupiravir 800mg median 0.1, range 0-0.3; vs. placebo median 0.2, range 0-0.4), and NEWS2 (molnupiravir 800mg median 0.5, range 0-1 vs. placebo median 0, range 0-1) in 1 study with 10 participants.[4] and by sustained recovery (molnupiravir 800mg RR 1.01 95% CI 0.69-1.47, 147 participants [7].

Other non-critical outcomes

The use of molnupiravir 800mg twice daily showed no significant decrease in infectious viral isolation by day 3 (RR 0.11, 95% CI 0.01, 1.02) and by day 5 (RR 0.11, 95% CI 0.01, 1.02) compared to placebo in 1 study with 107 participants.

Molnupiravir 800mg significantly reduced the time to viral RNA clearance compared to placebo (median 14 days, 95% CI 13-14 for molnupiravir 800mg; median 15 days, 95% 15-27 for placebo; p = 0.013). Subgroup analysis for seronegative patients showed significant reduction in time to viral RNA clearance among those given molnupiravir 800mg compared to placebo (median 14 days vs. 27 days in placebo, p = 0.001).[5]

Adverse events

Pooled estimate on the risk for adverse events showed no significant difference between molnupiravir and placebo (RR 0.92, 95% CI 0.82, 1.05; I^2 = 0%). There was also no significant difference on the risk for serious adverse events (RR 1.03, 95% CI 0.76, 1.40; I^2 = 0%). The most common adverse events reported were nausea, diarrhea, cough, loss of smell/taste, headache, insomnia, increased ALT levels, thrombocytopenia, and pneumonia.[4-5,7] Serious adverse events reported were decreased oxygen saturation, acute respiratory failure, and cerebrovascular accident.[5,7]

Evidence to Decision

A full treatment course of molnupiravir is estimated to cost Php 4,000 – 5,200.[9] The FDA granted emergency use authorization for molnupiravir as treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults 18 years old and above with a positive SARS-COV-2 diagnostic test and who are at risk for developing severe illness. [10]

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
Australian Guideline on COVID-19 as of December 22, 2021 [11]	The study from the MOVe-OUT Study Group is under review by the Taskforce and a recommendation will be published in early 2022.
Infectious Diseases Society of America (IDSA) as of December 28, 2021 [12]	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 5 days of symptom onset rather than no molnupiravir. (Conditional recommendation, Low certainty of evidence)
US-NIH Guidelines as of December 30, 2021 [13]	For nonhospitalized patients with mild to moderate COVID-19 who are at high risk of disease progression, the panel recommends using Molnupiravir 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years ONLY when none of the following options: nirmatrelvir with ritonavir, sotrovimab, remdesivir can be used (CIIa)

Surviving Sepsis Campaign Guidelines on the management of COVID-19 in the ICU as of January 29, 2021 [14]	No statement on the use of molnupiravir for the treatment of COVID-19.
WHO Living Guidelines as of December 7, 2021 [15]	

Research Gaps

There are thirteen (13) ongoing RCTs on molnupiravir registered in different trial registries (Appendix 7). Five (5) studies are for treatment of mild to severe COVID-19, while one (1) study is for prophylaxis. An update of this review will be done once results of these trials are available.

References

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[3] Painter W, 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 65:e02428-20. https://doi.org/10.1128/AAC.02428-20.

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[6] Caraco Y, et al. Phase 2/3 Trial of Molnupiravir for Treatment of Covid-19 in Nonhospitalized Adults. NEJM. 2021 December 16. DOI: 10.1056/EVIDoa2100043

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[8] Bernal A, da Silva, M.M, Masungie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martin-Quiros A, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. NEJM. 2021 December 16. DOI: 10.1056/NEJMoa2116044

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[11] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v48.0. Updated December 22, 2021. Available at https://app.magicapp.org/#/guideline/5619.

[12] Infectious Diseases Society of America. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Special update: Updated December 28, 2021. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/.

[13] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Updated December 30, 2021. Available at https://www.covid19treatmentguidelines.nih.gov/.

[14] Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First Update. Released 2021 January 29, Accessed 2022 January 1. https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19

[15] World Health Organization. Therapeutics and COVID-19 Living Guidelines. Updated December 7, 2021. Available at https://apps.who.int/iris/bitstream/handle/10665/345356/WHO-2019-nCoV-therapeutics-2021.3-eng.pdf.

Appendix 1. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND ("Molnupiravir" [Mesh] OR molnupiravir) Filter; Publication December 2021 to January 2022	January 5, 2022 4:57PM	16	2
CENTRAL	{MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR MeSH descriptor: [COVID-19] OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND MeSH descriptor: [Molnupiravir] explode all trees OR molnupiravir	January 5, 2022 5:16 PM	24	15
COVID-NMA Initiative	Molnupiravir	January 5, 2022 5:13PM	2	2
Google Scholar	Molnupiravir AND COVID AND randomized trial Since 2021	January 5, 2022 5:25 PM	9	5
ClinicalTrials.gov	Molnupiravir,COVID-19 , COVID-19 pneumonia, investigational studies	January 5, 2022 5:35PM	2	1
Chinese Clinical Trial Registry	Molnupiravir AND COVID	January 5, 2022 5:37PM	0	0
EU Clinical Trials Register	Molnupiravir AND COVID	January 5, 2022 5:39PM	0	0
Republic of Korea - Clinical Research Information Service	Molnupiravir	January 5, 2022 5:40PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Molnupiravir	January 5, 2022 5:41 PM	4	4
CenterWatch	Molnupiravir	January 5, 2022 5:43PM	2	2
Cochrane COVID-19 study register	Molnupiravir (last month)	January 5, 2022 5:48PM	2	1

chinaxiv.org	Molnupiravir	January 5, 2022 5:50	0	0
Medrxiv.org	Molnupiravir AND COVID Filter: December 1, 2021 to January 5, 2022	January 5, 2022 5:54 PM	10	0
Biorxiv.org	Molnupiravir AND COVID Filter: December 1, 2021 to January 5, 2022	January 5, 2022 5:59PM	21	0

Appendix 2. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase I, open-label, dose-escalating, randomized controlled trial Khoo et al, 2021 (UK) [4]	N = 18 Outpatients aged ≥ 18 years with RT-PCR confirmed COVID-19 within 5 days of symptom onset, mild or moderate disease (no uncontrolled chronic conditions) Follow-up: 29 days	Molnupiravir 1. 300mg BID x 5 d 2. 600mg BID x 5 d 3. 800mg BID x 5 d Standard of care	Primary outcome: Dose-limiting toxicity over 7 days Secondary outcomes: • Adverse events • Serious adverse events • Oxygen saturation • Mortality (up to day 29) • Patient reported outcome measure (FLU-PRO) • WHO COVID-19 ordinal scale • National Early Warning Score (NEWS2)	Randomized, open label
Molnupiravir for Oral Treatment of COVID-19 in non-hospitalized Patients Bernal et al, 2021 MOVe-OUT study group (20 Countries)	N = 1,411 Non-hospitalized adults with laboratory confirmed COVID-19 with 5 days of symptom onset Mild to moderate disease At least one risk factor for development of severe disease: • Age >60 years; • Active cancer; • Chronic kidney disease; • Chronic obstructive pulmonary disease; • Obesity, • Diabetes mellitus Follow-up: Day 29	Molnupiravir 800mg twice daily for 5 days Placebo	Primary outcomes: • Hospitalization • Mortality • Adverse events Secondary outcome: • WHO-11 point clinical progression	Double- blind placebo-controlled trial
Newly included studies				
Phase 2/3 Trial of Molnupiravir for Treatment of Covid-19 in Nonhospitalized Adults Caraco et al. 2021 MOVe-OUT study group (14 countries)	N=150 Laboratory confirmed Covid-19 with onset of Covid-19 signs and/or symptoms up to 7 days before randomization Mild to moderate disease All mild disease with at least one risk factor for development of severe disease: • age > 60 years • active cancer	Molnupiravir 1. 200mg BID x 5 d 2. 400mg BID x 5 d 3. 800mg BID x 5 d Placebo	Primary outcomes: • Hospitalization • Mortality • Adverse events Secondary outcome: WHO-11 point clinical progression	Double- blind placebo-controlled trial

	• chronic kidney disease • chronic obstructive pulmonary disease • immunocompromised status/solid organ transplant recipient • obesity • serious heart conditions • diabetes mellitus • sickle cell disease Follow-up: Day 29			
A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus Fischer et al, 2021 (USA)	N = 202 Outpatients aged > 18 years with RT-PCR confirmed COVID-19 within 7 days of symptom onset Mild or moderate disease Follow-up: 28 days	Molnupiravir 1. 200mg BID x 5 d 2. 400mg BID x 5 d 3. 800mg BID x 5 d Placebo	Primary outcomes: • Time to viral RNA clearance • Adverse events Secondary outcomes: • Time to infectious virus elimination • Median viral RNA change from baseline • Severity/duration of self-reported symptoms SARS-CoV-2 antibody detection	Double- blind placebo-controlled trial
Randomized Trial of Molnupiravir or Placebo in Patients Hospitalized with Covid-19 Arribas J, et al (2021) MOVe-IN study group (15 countries)	N= 154 Adult patients requiring in-hospital treatment laboratory confirmed COVID-19 within ≤10 days symptom onset Mild to severe Follow-up: 29 days	Molnupiravir 1. 200mg BID x 5 d 2. 400mg BID x 5 d 3. 800mg BID x 5 d Placebo	Primary outcomes • Adverse events • Serious adverse events Secondary outcomes: • Sustained Recovery • All-cause mortality	Double- blind placebo-controlled trial

Appendix 3. Study Appraisal

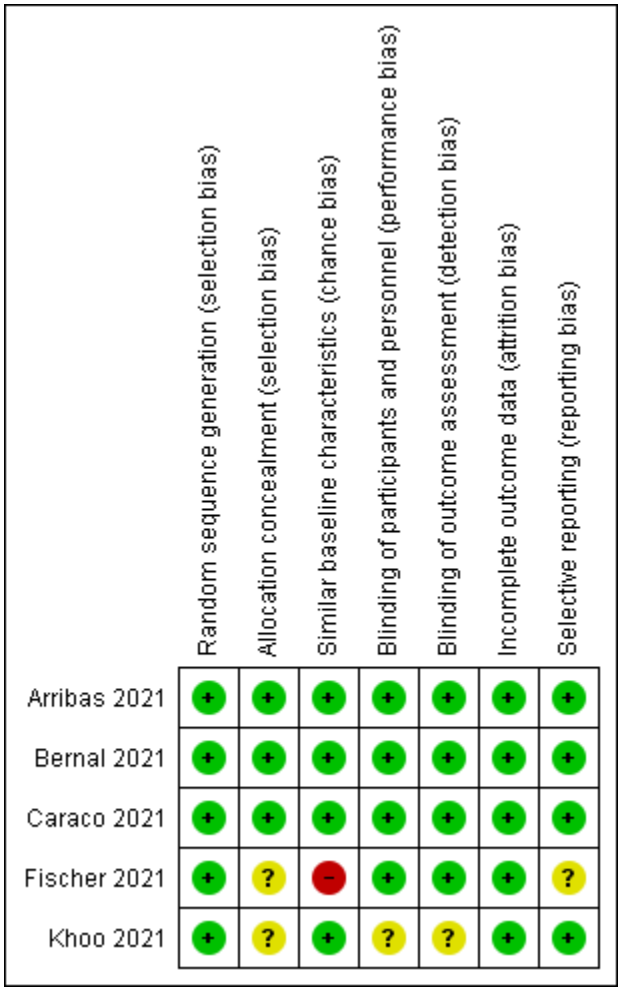

Figure 1. Risk of bias summary table

Appendix 4. GRADE Evidence Profile

Author(s): Katherine Ruth O. Relato, MD; Natasha Ann Esteban-Ipac, MD
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality, day 29												
4	randomised trials	serious[a]	not serious	not serious	serious[b]	none	7/912 (0.8%)	14/910 (1.5%)	**RR 0.51** (0.21 to 1.25)	**8 fewer per 1,000** (from 12 fewer to 4 more)	⨁⨁◯◯ Low	CRITICAL
All-cause mortality (mild-moderate, out-patient)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	3/840 (0.4%)	13/835 (1.6%)	**RR 0.23** (0.07 to 0.81)	**12 fewer per 1,000** (from 14 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
All-cause mortality (mild-severe, hospitalized)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	4/72 (5.6%)	1/75 (1.3%)	**RR 4.35** (0.47 to 39.92)	**45 more per 1,000** (from 7 fewer to 519 more)	⨁⨁⨁◯ Moderate	CRITICAL
Hospitalization												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	52/840 (6.2%)	73/835 (8.7%)	**RR 0.70** (0.50 to 0.99)	**26 fewer per 1,000** (from 44 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse Events												
5	randomised trials	serious[a]	not serious	not serious	not serious	none	302/917 (32.9%)	328/918 (35.7%)	**RR 0.92** (0.82 to 1.05)	**29 fewer per 1,000** (from 64 fewer to 18 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious Adverse Events												
5	randomised trials	serious[a]	not serious	not serious	serious[b]	none	76/917 (8.3%)	74/918 (8.1%)	**RR 1.03** (0.76 to 1.40)	**2 more per 1,000** (from 19 fewer to 32 more)	⨁⨁◯◯ Low	CRITICAL
Clinical Improvement												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[intervention]	[comparison]	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	not serious	none	312/709 (44.0%)	314/699 (44.9%)	**RR 0.98** (0.87 to 1.10)	**9 fewer per 1,000** (from 58 fewer to 45 more)	⨁⨁⨁⨁ High	CRITICAL
Isolation of infectious virus by day 3												
1	randomised trials	very serious[a,c,d]	not serious	not serious	serious[b,e]	none	1/53 (1.9%)	3/18 (16.7%)	**RR 0.11** (0.01 to 1.02)	**148 fewer per 1,000** (from 165 fewer to 3 more)	⨁◯◯◯ Very low	IMPORTANT
Isolation of infectious virus by day 5												
1	randomised trials	very serious[a,c,d]	not serious	not serious	serious[b,e]	none	1/53 (1.9%)	3/18 (16.7%)	**RR 0.11** (0.01 to 1.02)	**148 fewer per 1,000** (from 165 fewer to 3 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Dissimilar baseline characteristics of the treatment groups despite randomization. The molnupiravir group had a higher baseline prevalence of SARS-CoV-2 antibody (30-35.3% vs. 18.2% in placebo)
b. Wide confidence interval
c. Reporting bias
d. Attrition bias (missing outcome data)
e. Low sample size, does not reach optimal information size

Appendix 5. Forest Plots

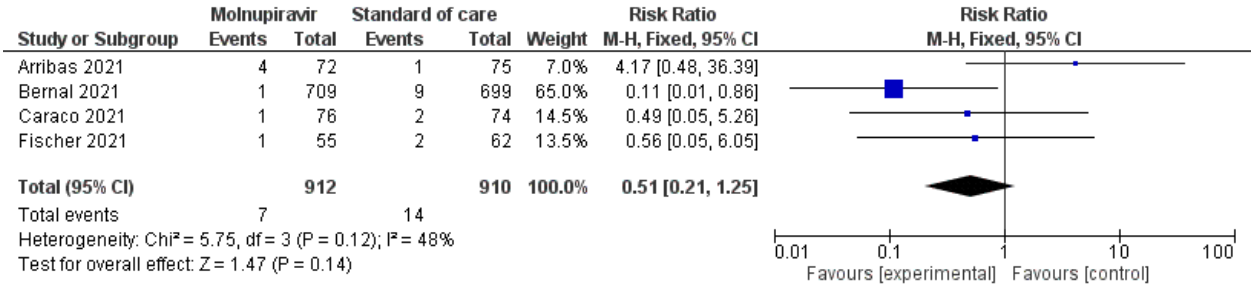

Figure 1. All-cause mortality Day 29

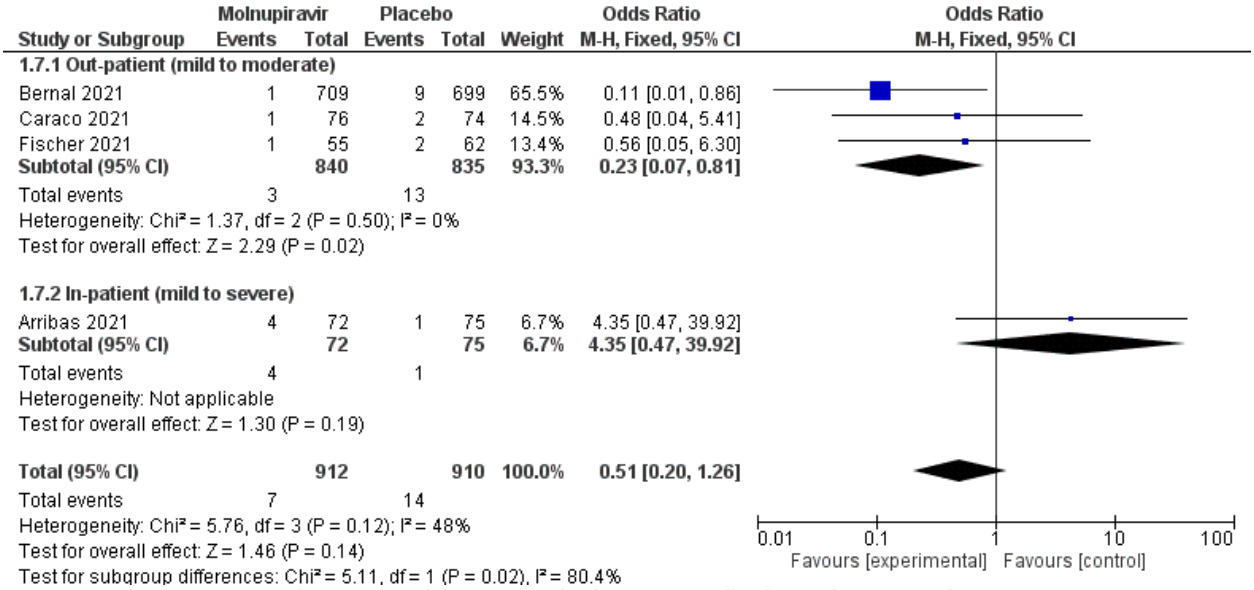

Figure 2. Subgroup analysis on mortality based on severity

Figure 3. Hospitalization

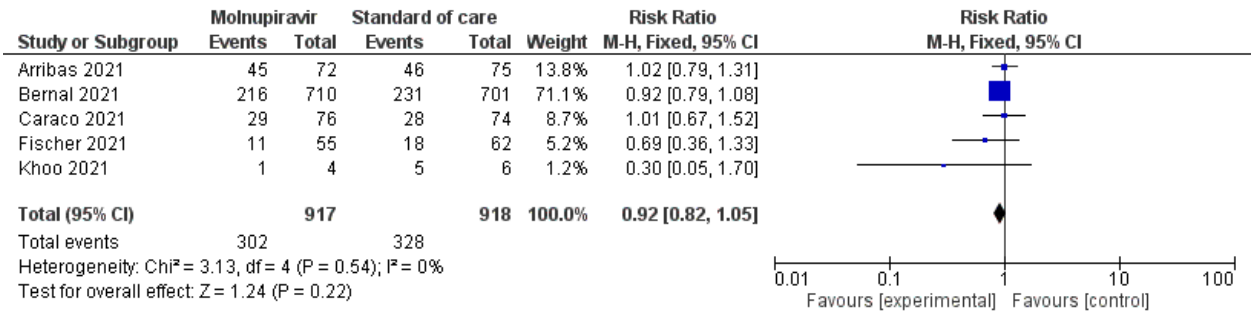

Figure 4. Adverse Events

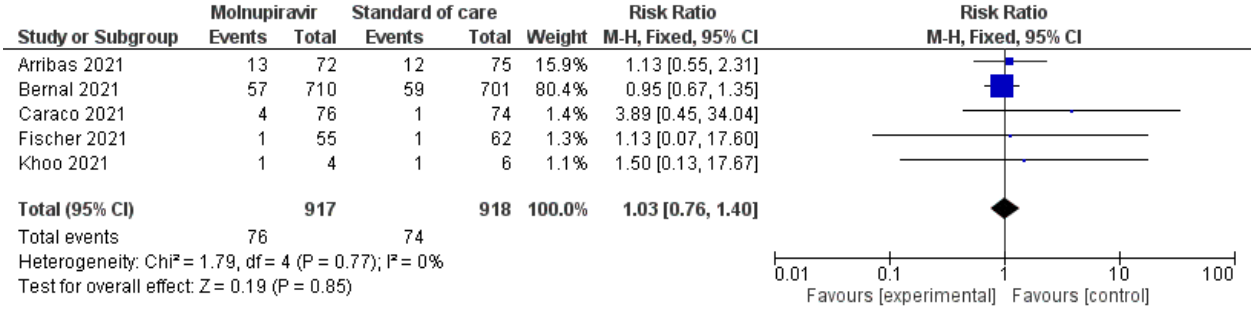

Figure 5. Serious Adverse Events

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Study of MK-4482 for Prevention of Coronavirus Disease 2019 (COVID-19) in Adults (MOVe-AHEAD)	N = 1,332 Age ≥ 18 Does not have confirmed or suspected COVID-19 Lives in a household with an index case where the index case is a person with documented COVID-19 Must have: 1. A first positive SARS-CoV-2 test result from a sample collected within ≤5 days prior to randomization of the participant, and 2. At least 1 symptom attributable to COVID-19	Molnupiravir 800mg PO BID x 5 days Placebo (matching)	Primary outcomes: • Percentage of participants who develop COVID-19 (up to day 14) • Adverse events • Discontinuation rate due to adverse events Secondary outcomes: • Percentage of participants who develop COVID-19 (up to day 29) • RT-PCR positivity rate (up to day 14)	Randomized controlled trial
2. A prospective, randomized, parallel, multicentric, phase-III clinical trial of Molnupiravir 800 mg capsules and standard of care (SOC) compared to standard of care only in confirmed RT-PCR positive patients with mild COVID-19 (NOCOV)	N = 1,218 Age: 18 to 60 years old Confirmed COVID-19 infection (mild)	Molnupiravir 200mg PO BID x 5 days Standard of care (includes Ivermectin)	Primary outcome: • Hospitalization rate (up to day 14) Secondary outcomes: • Hospitalization rate (up to day 28) • Time to clinical improvement • Mortality (day 14) • RT-PCR negativity (day 10, day 15) • Adverse events	Randomized controlled trial
3. MK-4482 Ph 2/3 Study in Hospitalized Adults with COVID-19	N = 1,300 Age ≥ 18 Confirmed COVID-19 infection (mild, moderate, or severe) Initial onset of symptoms ≤ 10 days prior to randomization. At least 1 sign/symptom attributable to COVID-19	Molnupiravir x 5 days Placebo (matching)	Primary outcomes: • Time-to-sustained recovery (up to day 29) • Adverse events • Discontinuation rate due to adverse events Secondary outcomes: • Mortality (up to day 29) • Pulmonary score • WHO clinical progression scale	Randomized controlled trial

Study Title	Patients (n)	Interventions	Outcomes	Method
4. Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adults Participants with COVID-19	N = 1,850 Age ≥ 18 Confirmed COVID-19 infection (mild, moderate or severe) Onset of signs/symptoms attributable to COVID-19 for ≤5 days prior At least 1 characteristic or underlying medical condition associated with an increased risk of severe illness from COVID-19	Molnupiravir 200mg PO BID x 5 days 400mg PO BID x 5 days 800mg PO BID x 5 days Placebo (matching)	Primary outcomes: • Hospitalization rate (up to day 29) • 29-day mortality • Adverse events • Discontinuation rate due to adverse events Secondary outcomes: • Time to sustained resolution or improvement of symptoms • Time to progression of symptoms • WHO clinical progression scale	Randomized controlled trial
5. A phase II/III clinical trial to understand the efficacy and safety of Molnupiravir 800 mg in the treatment of patients diagnosed with moderate COVID-19	Age 18 to 60 years old Confirmed COVID-19 infection (moderate)	Molnupiravir 800 mg BID Standard of care	Primary outcome: Clinical improvement at day 14	Randomized controlled trial
6. The safety of Molnupiravir and its effect on viral shedding of SARS-CoV-2 (END-COVID)	N = 96 Age ≥ 18 Confirmed COVID-19 infection Admitted in the hospital, anticipated to remain for ≥ 24 hours	Molnupiravir BID x 5 days Placebo	Virologic clearance (day 28) Adverse events Serious adverse events	Randomized controlled trial
7. Study to evaluate the efficacy and safety of Molnupiravir capsules Compare with the with Standard of Care Medications Care alone in patients who are suffering with Moderate COVID-19 disease	Age 18 to 60 years old Confirmed COVID-19 infection with presence of clinical features of dyspnea and or hypoxia, fever, cough with a risk factor for progressing to severe COVID-19	Molnupiravir 1600mg BID Standard of care	Clinical improvement at Day 14 Clinical improvement at Day 28	Open label randomized controlled trial
8. A Clinical Study to Test the Use of Capsule Molnupiravir in COVID-19 Patients with Mild Symptoms and without Lung Involvement	Age 18-60 years old Confirmed COVID-19 patient with mild COVID-19	Molnupiravir 800mg q12 for 5 days Standard of care	Adverse Events Mortality Clinical Improvement Viral negative conversion	Open label randomized controlled trial

	disease without any evidence of breathlessness.			
9. Clinical Trial to Evaluate the Efficacy and Safety of Molnupiravir Capsule in Treatment of Subjects with Moderate Coronavirus Disease (COVID-19)	Age 18-60 years old Confirmed COVID-19 patient Moderate COVID 19	Molnupiravir 800mg q12 for 5 days Standard of care	Clinical Improvement Day 14	Open label randomized controlled trial
10. A Prospective, Randomized, Multicenter, Open Label, Parallel Group Study To Evaluate Safety And Efficacy Of Oral Molnupiravir As Add On To Standard Of Care For Treatment Of Mild Patients With Covid-19 Disease	N = 1,218 Age 18-60 years old Confirmed COVID-19 patient Mild COVID 19	Molnupiravir 800mg q12 for 5 days Standard of care	Rate of hospitalization Day 14	Open label randomized controlled trial
11. A Clinical Study with Molnupiravir Capsules 800mg in COVID-19 Patients with Mild symptoms.	N = 1,220 Age 18-60 years old Confirmed COVID-19 patient Mild COVID 19	Molnupiravir 800mg q12 for 5 days Standard of care	Rate of hospitalization Day 14	Open label randomized controlled trial
12. MK4482-013 Phase 3 Study for Prevention of COVID-19 in Adults Spain	N = 1,340 Age 18 years and above Confirmed COVID-19 patient	Molnupiravir Placebo	Progression to severe disease day 14 Adverse event	Randomized double blind placebo controlled trial
13. Single and Multiple Dose Study of MK-4482 in Healthy Japanese Adults	N = 72 Age 20-60 years old previously healthy Confirmed COVID-19 patients	Molnupiravir 100-1600 mg BID for 11 doses Placebo	Adverse events	Randomized double blind placebo controlled trial