EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 patients, should molnupiravir be used for treatment?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of molnupiravir within 5 days of symptom onset in adult patients with COVID-19 infection who are non-oxygen requiring and with at least one risk factor* for progression. *Risk factors for progression include: age >60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity, serious heart conditions, or diabetes mellitus	Very low	Weak
We suggest against the use of molnupiravir among children with COVID-19.	Very low	Weak

Consensus Issues

Molnupiravir showed no significant benefit on critical outcomes (all-cause mortality, clinical improvement, need for hospitalization, and serious adverse events). Although there is evidence of benefit on the subgroup analysis of the need for hospitalization on unvaccinated participants, the panel took into consideration that the study on vaccination may not be reflective of the vaccination status in our country since 90% of the participants in the study are vaccinated with three doses. Another consideration is the duration of the last dose of vaccination since immunity may wane depending on the time it was given. The panel also noted that there is benefit on subgroup analysis on all-cause mortality among the mild to moderate non-hospitalized patients. However, because of the current definition of moderate COVID-19 in our guideline, the panel emphasized that the studies only included the non-oxygen requiring participants, hence specifying it as part of the recommendation to avoid confusion.

Children are a vulnerable population since there is no evidence for the use of molnupiravir and there is still no FDA recommendation for the use of molnupiravir in children with COVID-19, suggesting against the use of molnupiravir will be beneficial for children.

KEY FINDINGS

- Eleven (11) randomized controlled trials (RCTs) studied the effect of molnupiravir on the treatment of COVID-19 compared to standard of care and/or placebo.
- Molnupiravir did not significantly decrease the all-cause mortality 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. Subgroup analysis on mortality based on vaccination did not show significant benefit across subgroups.
- Molnupiravir did not show significant reduction in the need for hospitalization at day 29 compared to standard of care and/or placebo. Subgroup analysis based on vaccination status in need for hospitalization show significant benefit on unvaccinated subgroup but did not show significant benefit on vaccinated subgroup.
- Molnupiravir did not show significant benefit on clinical improvement and need for mechanical ventilation compared to standard of care and/or placebo.
- Molnupiravir did not show increase in clinical improvement based on WHO progression scale of 1 or less at day 15 and day 29.
- There was no significant benefit of the use of molnupiravir in viral negative conversion at day 7 and emergency room visit/acute care visit at day 29 compared to standard of care and placebo.
- Adverse events and serious adverse events were similar between molnupiravir and standard of care and/or placebo.
- The over-all risk of bias was downgraded to very low due to serious risk of bias, serious inconsistency, and serious imprecision.

WHAT'S NEW IN THIS VERSION?

Six (6) new RCTs (Butler 2022, Johnson 2022, Khoo 2022, Kumarasamy 2022, Tippabhotla 2022 and Zou 2022) are included in this update. One of the studies is a preprint (Tippabhotla 2022).

PREVIOUS RECOMMENDATION
As of 19 February 2021

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).

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

A systematic search was done from January 5, 2022 to January 9, 2023 using Pubmed, Cochrane Library, and Google Scholar 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.

RESULTS

Characteristics of included studies

Eleven (11) randomized controlled clinical trials (RCTs) (N=31,792) investigated the effectiveness of molnupiravir among confirmed COVID-19 patients compared to placebo and/or standard of care. One of the 11 trials is a preprint. The summary on the characteristics of included studies can be found in Appendix 3. No available studies were found for children or adolescents.

Four studies are done in multinational sites (Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Italy, Japan, Mexico, Philippines, Russian Federation, South Africa, Spain, Taiwan, UK, Ukraine, and USA) [4-7]. Three studies are done in the UK [8-10], two studies are done in India [11-12], one study is done in the US [13] and one study is done in China [14]. Study participants in nine trials were non-hospitalized mild to moderate COVID-19 patients [4,5,7-13]. While two studies included mild to severe hospitalized patients [6,14]. Five 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) [4,5,6,10,12]. Eight studies included symptom onset within 5 days of randomization [4,7-12,14], while two studies included symptom onset within 7 days [5,13] and one study included symptom onset within 10 days [6]. Two studies included vaccinated participants [10,14], while five studies excluded vaccinated participants [4,6,7,12,13]. One study included both vaccinated and unvaccinated participants [9]. One study included confirmed COVID-19 with Omicron variant [14]. 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]. Seven studies compared molnupiravir given 800mg twice daily for 5 days to placebo [2,7,9-12,14]. Only the results of molnupiravir given 800mg twice daily for 5 days in the studies compared to standard of care and/or placebo were pooled. All of the studies administered molnupiravir orally or via nasogastric tube.

Certainty of evidence

The overall certainty of evidence was rated very low due to serious risk of bias, serious inconsistency, and serious imprecision on two of the critical outcomes (need for hospitalization and clinical improvement). The

serious risk of bias was due to selection bias, performance bias, and detection bias. The risk of bias table is in Appendix 4. The GRADE Evidence profile is detailed in Appendix 5.

Critical outcomes

Molnupiravir did not show significant benefit in the all-cause mortality at day 29 (RR 0.45 95% CI 0.20-1.03; I^2=17%; 10 RCTs, n=30,831) compared to standard of care and placebo. However, subgroup analysis on mortality based on severity showed significant benefit of molnupiravir on outpatient with mild to moderate diseases at day 29 (RR 0.30 95% CI 0.11-0.81; I^2=0%; 9 RCTs, 30,227 participants) and no significant benefit on hospitalized, mild to severe diseases at day 29 (RR 3.08 95% CI 0.33-28.95; 1 RCT, 154 participants). Subgroup analysis on mortality based on vaccination status did not show significant benefits across groups, including those unvaccinated (RR 0.39 95% CI 0.14-1.09; I^2=36%; 5 RCTs, 3,074 participants) and those vaccinated (RR 0.61 95% CI 0.14-2.54; 2 RCTs, 25,998 participants)

Moreover, molnupiravir did not show significant reduction in the need for hospitalization at day 29 (RR 0.68, 95% CI 0.46-1.02; I^2=51%; 7 RCTs, 30,101 participants) compared to standard of care and placebo. Subgroup analysis on the effect of molnupiravir on the need for hospitalization stratified according to vaccination status showed significant reduction in hospitalization among the unvaccinated subgroup (RR 0.69, 95% CI 0.50-0.95; I^2=0%; 4 RCTs, 2,920 participants) and did not show significant benefit on the need for hospitalization among the vaccinated subgroup (RR 1.12 95% CI 0.85-1.48; 1 RCT, 25,783 participants).

Molnupiravir did not show significant benefit in clinical improvement at day 14 to 29 (RR 1.11 95% CI 0.98-1.25; I^2=98%; 3 RCTs, 28,221 participants) compared to standard of care and placebo, with significant heterogeneity. Also, molnupiravir did not show significant benefit on clinical improvement based on WHO progression scale of equal or less than 1 (asymptomatic and ambulatory) by day 15 (RR 1.13 95% CI 0.92-1.39; I^2=0%; 3 RCTs, 1,745 participants) and day 29 (RR 1.00 95% CI 0.91-1.11; I^2=0%; 3 RCTs, 1,745 participants) compared to standard of care and placebo.

Other non-critical outcomes

Molnupiravir did not show significant reduction in emergency room visit or acute care visit (RR 0.87, 95% CI 0.57-1.33; I^2=83%; 2 RCTs, 27,194 participants) compared to standard of care and placebo, with significant heterogeneity.

Molnupiravir show no significant reduction in the need for oxygen supplementation (RR 0.75 95% CI 0.47-1.22; 1 RCT; 1,411 participants) compared to standard of care and placebo, however, Molnupiravir showed significant reduction in the need for mechanical ventilation (RR 0.32 95% CI 0.12-0.90; 1 RCT; 1,411 participants) compared to standard of care and placebo.

The use of molnupiravir 800mg twice daily showed no significant benefit in viral negative conversion by day 7 (RR 1.50 95% CI 0.49-4.55; I^2=99% 8 RCTs; 3,241 participants) compared to standard of care and placebo, but with significant heterogeneity.

Adverse events

Pooled estimate on the risk for adverse events showed no significant difference between molnupiravir and placebo (RR 0.99, 95% CI 0.89-1.09; I^2=13%). There was also no significant difference on the risk for serious adverse events (RR 0.88, 95% CI 0.69-1.12; I^2=3%). The most common adverse events reported were nausea, diarrhea, abdominal pain, chest pain, cough, loss of smell/taste, headache, insomnia, skin rash, increased ALT levels, thrombocytopenia, and pneumonia [4-5,7,8,11,12,14]. Serious adverse events reported were decreased oxygen saturation, acute respiratory failure, and cerebrovascular accident [5,7, 8].

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendations	Strength of Recommendation / Certainty of Evidence
Australian Guideline on COVID-19 as of December 20, 2022 [17]	Do not routinely use molnupiravir for the treatment of COVID-19.	Conditional recommendation against
	Do not use molnupiravir for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomized trials with appropriate ethical approval.	
	Do not use molnupiravir for the treatment of COVID-19 in children and adolescents outside of randomized trials with appropriate ethical approval.	
Infectious Diseases Society of America (IDSA) Guidelines as of November 21, 2022 [18]	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 28, 2022 [19]	The COVID-19 Treatment Guidelines Panel (the Panel) recommends using molnupiravir 800mg orally (PO) twice daily for 5 days as an alternative therapy in non-hospitalized patients aged ≥18 years with mild to moderate COVID-19 who are at high risk of disease progression ONLY when ritonavir-boosted nirmatrelvir (Paxlovid) and remdesivir are not available, feasible to use, or clinically appropriate; treatment should be initiated as soon as possible and within 5 days of symptom onset.	Weak recommendation
	The Panel recommends against the use of molnupiravir for the treatment of COVID-19 in pregnant patients unless there are no other options and therapy is clearly indicated.	Strong recommendation
	People who engage in sexual activity that may result in conception should use effective contraception during and following treatment with molnupiravir.	
	Alternative therapy. For use when the preferred therapies (Ritonavir-boosted nirmatrelvir (Paxlovid) and Remdesivir) are not available, feasible to use, or clinically appropriate.	
WHO Living Guidelines as of January 13, 2023 [20]	We suggest treatment with molnupiravir for patients with non-severe COVID-19 at highest risk of hospitalization (excluding pregnant and breastfeeding women, and children).	Conditional recommendation

ONGOING STUDIES AND RESEARCH GAPS

There are twenty four (24) ongoing RCTs on molnupiravir registered in different trial registries (Appendix 7). Nineteen (19) studies phase 3 trials. One is a large trial which includes children in the population. An update of this review will be done once results of these trials are available.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

A full treatment course of molnupiravir is estimated to cost ₱2,800 to ₱5,000. 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 [15]. In a study done by Goswani et. al published in 2022 for the cost effectiveness of molnupiravir versus best supportive care on outpatient adult COVID-19 patients in the United States, per patient quality adjusted life years was increased by the use of molnupiravir compared to best supportive care. Per patient total healthcare cost over the lifetime horizon was also reduced by approximately ₱51,800($895) [16].

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Appendix 1. Preliminary Evidence to Decision

Table 2. Summary of initial judgments prior to the panel discussion (N=6/10)

FACTORS	JUDGMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					• Yes, COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large (2)	Moderate (3)	Small (1)	Trivial	Varies	Uncertain	• Molnupiravir did not show significant benefit in the all-cause mortality at day 29 (RR 0.45 95% CI 0.20 to 1.03) Subgroup analysis showed significant benefit among out-patient with mild to moderate diseases at day 29 (RR 0.30 95% CI 0.11to 0.81) but no significant benefit on hospitalized, mild to severe diseases at day 29 (RR 3.08 95% CI 0.33 to 28.95). Subgroup analysis according to vaccination did not show significant benefit across groups. • Molnupiravir had no benefit on need for hospitalization at D29 (RR 0.68, 95% CI 0.46 to 1.02). Subgroup analysis showed benefit among unvaccinated subgroup (RR 0.69, 95% CI 0.50 to 0.95) but not among vaccinated subgroup (RR 1.12 95% CI 0.85 to 1.48) • Molnupiravir had no benefit on clinical improvement.
Harm	Large (1)	Moderate (1)	Small (3)	Trivial (1)	Varies	Uncertain	• Molnupiravir showed no significant difference on adverse event (RR 0.99, 95% CI 0.89 to 1.09 and serious adverse event (RR 0.88, 95% CI 0.69 to 1.12). • The most common adverse events reported were nausea, diarrhea, abdominal pain, chest pain, cough, loss of smell/taste, headache, insomnia, skin rash, increased ALT levels, thrombocytopenia, and pneumonia. • Serious adverse events reported were decreased oxygen saturation, acute respiratory failure, and cerebrovascular accident

Certainty of Evidence	High	Moderate	Low (2)	Very low (4)			• The overall quality of evidence was rated very low due to serious risk of bias, serious inconsistency and serious imprecision on one critical outcome (hospitalization).
Balance of effects	Favors intervention (2)	Probably favors intervention (4)	Does not favor intervention	Probably favors no intervention	Favors no intervention	Varies	• Molnupiravir showed no potential harm since there is no significant difference in the adverse event and inconclusive result on serious adverse event. With the balance favoring benefit in the reduction of the all-cause mortality among outpatients, and reduction in hospitalization among unvaccinated individuals.
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (2)	Probably no important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (1)	Moderate Cost (4)	Negligible cost or savings	Moderate savings (1)	Large savings	• A full treatment course of molnupiravir is estimated to cost Php 2,800 to 5,000.
Certainty of evidence of required resources	No included studies (4)	Very low (2)	Low	Moderate	High		
Cost effectiveness	No included studies	Favors using the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the invention (4)	Favors the intervention (2)	• n a study done by Goswani et. al published in 2022 for the cost effectiveness of molnupiravir versus best supportive care on outpatient adult COVID-19 patients in the United States, per patient quality adjusted life years was increased by the use of molnupiravir compared to best supportive care. Per patient total healthcare cost over the lifetime horizon was also reduced by approximately ₱51,800.
Equity	Uncertain	Varies (3)	Probably reduced (2)	Probably no impact	Probably increased (1)	Increased	

Acceptability	Uncertain	Varies	No	Probably no	Probably yes (5)	Yes (1)	
Feasibility	Uncertain	Varies	No	Probably no	Probably yes (3)	Yes (3)	• 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.
Recommendation	For (6)	Against					Additional considerations: More studies in the local setting and on pediatric patients would be much appreciated
Strength	Weak (5)	Strong (1)					

Appendix 2: Search and Yield 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 January 2022 to January 2023	January 9, 2023 10:02 PM	314	6
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 9, 2023 10:30PM	51	6
COVID-NMA Initiative	Molnupiravir	January 9, 2023 11:20PM	6	6
Google Scholar	"Molnupiravir"AND "COVID" AND "randomized trial" Since 2022	January 9, 2023 10:40PM	404	6
ClinicalTrials.gov	Molnupiravir,COVID-19 , COVID-19 pneumonia, investigational studies	January 9, 2023 11:27PM	10	0
Chinese Clinical Trial Registry	Molnupiravir AND COVID	January 9, 2023 11:29PM	1	0
EU Clinical Trials Register	Molnupiravir AND COVID	January 9, 2023 11:31PM	0	0
Republic of Korea – Clinical Research Information Service	Molnupiravir	January 9, 2023 11:33PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Molnupiravir	January 9, 2023 11:34 PM	5	1
CenterWatch	Molnupiravir	January 9, 2023 11:36PM	6	0
Cochrane COVID-19 study register	Molnupiravir	January 9, 2023 11:38PM	45	3

chinaxiv.org	Molnupiravir	January 9, 2023 11:40PM	0	0
Medrxiv.org	Molnupiravir AND COVID Filter: January 5, 2022 to January 9, 2023	January 9, 2023 11:44PM	78	1
Biorxiv.org	Molnupiravir AND COVID Filter: January 5, 2022 to January 9, 2023	January 9, 2023 11:46PM	54	0

Appendix 3: Characteristics of Included Studies

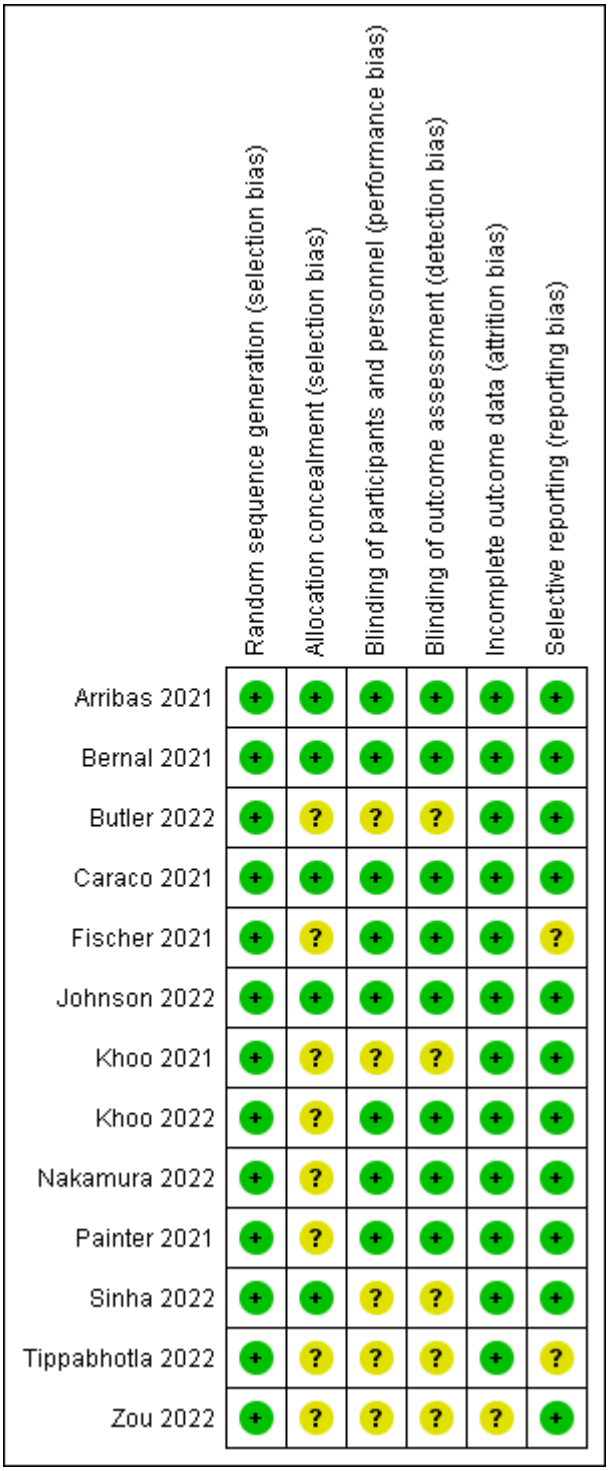
Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase I, open-label, dose-escalating, randomized controlled trial AGILE Khoo et al, 2021 (UK) [4] Phase Ib	N = 10 Age > 18 years old Out-patient Confirmed COVID-19 mild or moderate disease within 5 days of symptom onset no uncontrolled chronic conditions Follow-up: 29 days Enrollment: July 17, 2020 to October 30, 2020	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)	open label adaptive Randomized, controlled trial
Molnupiravir for Oral Treatment of COVID-19 in non-hospitalized Patients Bernal et al, 2021 MOVe-OUT study group (20 Countries) Phase 3	N = 1,433 Adults Non-hospitalized confirmed COVID-19 Mild to moderate disease with 5 days of symptom onset 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 Exclusion: need for hospitalization SARSCOV2 vaccination Follow-up: Day 29 Enrollment: May 6, 2021 to November 4, 2021	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
Phase 2/3 Trial of Molnupiravir for Treatment of Covid-19 in Nonhospitalized Adults Caraco et al. 2021 MOVe-OUT study group (14 countries) Phase 2/3	N=150 Adult Out-patient confirmed Covid-19 Mild to moderate disease with onset of symptoms up to 7 days All mild disease with at least one risk factor for development of severe disease: • age > 60 years • active cancer • chronic kidney disease • chronic obstructive pulmonary disease • immunocompromised status/solid organ transplant	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 (Day 29) Secondary outcome: WHO-11 point clinical progression	Double- blind placebo-controlled trial

	recipient ● obesity ● serious heart conditions ● diabetes mellitus ● sickle cell disease Exclusion: need for hospitalization Follow-up: Day 29 Initiated: October 2020			
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) Phase 2a	N = 117 Aged > 18 years Outpatients confirmed COVID-19 Mild or moderate disease within 7 days of symptom onset Unvaccinated <u>Follow-up</u>: 28 days Enrollment: June 19, 2020 to January 21, 2021	Molnupiravir 1. 200mg BID x 5 d 2. 400mg BID x 5 d 3. 800mg BID x 5 d Placebo	<u>Primary outcomes:</u> ● Time to viral RNA clearance ● Adverse events <u>Secondary outcomes:</u> ● 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) Phase 2/3	N= 154 Adult hospitalized confirmed COVID-19 within ≤10 days symptom onset Unvaccinated Mild to severe Exclusion: SARSCOV2 vaccination Follow-up: 29 days Enrollment: October 19, 2020 to January 12, 2021	Molnupiravir ● 200mg BID x 5 d ● 400mg BID x 5 d ● 800mg BID x 5 d Placebo	<u>Primary outcomes</u> ● Adverse events ● Serious adverse events <u>Secondary outcomes:</u> ● Sustained Recovery ● <u>All-cause mortality</u>	Double- blind randomized placebo-controlled trial
New Studies				
Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC) Butler, C et. Al (2022) UK Phase 3	N = 25,783 Age > 18 years with comorbidities: ● Chronic respiratory disease ● Chronic heart or vascular disease ● Chronic liver disease ● Chronic neurologic disease ● Severe and profound learning disability ● Down's syndrome ● Diabetes Mellitus ● Immunosuppression ● Transplant recipient ● Morbid obesity (BMI>35) ● Severe mental illness ● Care home resident	Molnupiravir 800mg BID x 5 days Standard of care	<u>Primary outcome:</u> <u>All-cause hospitalization</u> <u>Mortality</u> <u>Secondary outcome:</u> <u>Self-reported recovery</u>	Open-label adaptive randomized controlled trial

	Age 50 years or older Out-patient Confirmed COVID-19 Mild to moderate onset of symptoms ≤ 5 days vaccinated Follow up: Day 28 Enrollment: Dec 8, 2021 to April 27, 2022			
Effect of Molnupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19 MOVe-OUT Johnson, M et. Al (2022) (20 countries) Phase 3	N= 1,411 Age 18 years or older Nonhospitalized Confirmed COVID-19 Mild to moderate disease ≤ 5 days onset of signs or symptoms At least 1 risk factor for progression to severe disease ● age > 60 years ● active cancer ● chronic kidney disease ● chronic obstructive pulmonary disease ● immunocompromised status/solid organ transplant recipient ● obesity ● serious heart conditions ● diabetes mellitus Unvaccinated Exclusion: need for inpatient treatment SARSCOV2 vaccine Follow-up: Day 29 Study completion: May 5, 2022	Molnupiravir 800mg twice daily for 5 days Placebo	The use of respiratory interventions (conventional oxygen therapy, a high flow device, non-invasive mechanical ventilation) Acute care visit	Double- blind placebo-controlled trial
Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2) Khoo, S et al (2022) UK Phase 2	N = 180 Age > 18 years old Outpatients Confirmed COVID-19 mild or moderate disease within 5 days of symptom onset no uncontrolled chronic conditions Vaccinated and unvaccinated Exclusion: need for hospitalization Follow-up: 29 days Enrollment: Nov 18, 2020 to March 16, 2022	Molnupiravir 800mg twice daily for 5 days Placebo	Primary Outcome: Randomization to negative RT PCR Secondary Outcome: WHO progression scale Overall survival Mortality Hospitalization Adverse events Serious Adverse Events	Double-blind randomized placebo-controlled trial

Phase III trial of molnupiravir in adults with mild SARS-COV-2 infection in India Sinha S et al 2022 India Phase 3	N =1,218 Age 18-60 years old Out-patient Confirmed COVID-19 within 5 days of symptom onset Mild disease Without evidence of breathlessness Exclusion: Need for hospitalization Follow-up: day 28 Enrollment: May 2021 to August 2021	Molnupiravir 800mg BID x 5 days Standard of care	Primary outcome: Hospitalization Day 14 Secondary outcome: 2-point improvement in WHO progression scale Rate of SARS-COV2 RT PCR negativity Adverse Events	Open-label randomized control trial
Efficacy and safety of molnupiravir for the treatment of non-hospitalized adults with mild COVID-19 et al Tippabhotla K et al 2022 India Preprint Phase 3	N= 1220 Age 18-60 years old Non-hospitalized Confirmed COVID-19 Within 5 days symptom onset Mild disease with risk factors for progressing to severe disease Exclusion: need for hospitalization SARSCOV2 vaccination Follow-up Day 28 Enrollment: July 01, 2021 to August 24, 2021	Molnupiravir 800mg BID x 5 days Standard of care	Primary outcome; Hospitalization Day 14 Secondary outcomes: Hospitalization Day 28 Clinical Improvement (2-point decrease in WHO progression scale) SARS COV2 RT PCR negativity Mortality	Open label randomized controlled trial
Antiviral Efficacy and Safety of Molnupiravir Against Omicron Variant Infection: A Randomized Controlled Clinical Trial Zou, R et al 2022 China Phase 2	N = 116 Age 18-80 years old In-hospital Confirmed COVID-19 Positive for Omicron variant ≤ 5 days onset of signs or symptoms Mild to moderate Vaccinated Follow-up: Day 10 Enrollment: March 3 to 21 March 2022	Molnupiravir 800mg x 5 days Standard of Care	Primary outcome: Time to viral clearance Secondary outcome: Percentage of patients with negative SARS-COV2 virus on days 5, 7 and 10 Adverse events	Open label randomized controlled trial

Appendix 4: Study Appraisal (Risk of Bias Summary)



Appendix 5: GRADE Evidence Profile

Author: Katherine Ruth O. Relato, MD
Question: Molnupiravir compared to Standard of care or placebo for COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Molnupiravir	Standard of care or placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality												
10	randomised trials	serious[a]	not serious	not serious	serious[b,c]	none	7/15136 (0.0%)	17/15245 (0.1%)	**RR 0.40** (0.20 to 1.03)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Hospitalization												
7	randomised trials	serious[a,d]	serious[e]	not serious	serious[c]	none	171/14976 (1.1%)	212/15125 (1.4%)	**RR 0.68** (0.46 to 1.02)	**4 fewer per 1,000** (from 8 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Adverse Event												
9	randomised trials	serious[a,d]	not serious	not serious	not serious	none	485/2315 (21.0%)	493/2283 (21.6%)	**RR 0.99** (0.89 to 1.09)	**2 fewer per 1,000** (from 24 fewer to 19 more)	⨁⨁⨁◯ Moderate	CRITICAL
Serious Adverse Events												
9	randomised trials	serious[a,d]	not serious	not serious	serious[c]	none	117/15075 (0.8%)	133/15167 (0.9%)	**RR 0.88** (0.69 to 1.12)	**1 fewer per 1,000** (from 3 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL
Clinical Improvement												
3	randomised trials	serious[a,d]	serious[f]	not serious	serious[c]	none	9682/14039 (69.0%)	8363/14182 (59.0%)	**RR 1.11** (0.98 to 1.25)	**65 more per 1,000** (from 12 fewer to 147 more)	⨁◯◯◯ Very low	CRITICAL
Emergency room visit/Acute care visit												
2	randomised trials	serious[a,d]	serious[g]	not serious	serious[c]	none	759/13531 (5.6%)	748/13663 (5.5%)	**RR 0.88** (0.57 to 1.35)	**7 fewer per 1,000** (from 24 fewer to 19 more)	⨁◯◯◯ Very low	CRITICAL
Need for oxygenation												
1	randomised trials	not serious	not serious	not serious	not serious	none	31/710 (4.4%)	40/701 (5.7%)	**RR 0.75** (0.47 to 1.22)	**14 fewer per 1,000** (from 30 fewer to 13 more)	⨁⨁⨁⨁ High	CRITICAL
Need for mechanical ventilation												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	5/710 (0.7%)	15/701 (2.1%)	**RR 0.33** (0.12 to 0.89)	**14 fewer per 1,000** (from 19 fewer to 2 fewer)	⨁⨁⨁◯ Moderate	CRITICAL

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

Explanations

a. selection bias and performance bias
b. low event rate
c. wide confidence interval
d. reporting bias
e. I2= 51%
f. I2=98%
g. I2=81%

Appendix 6: Forest Plots

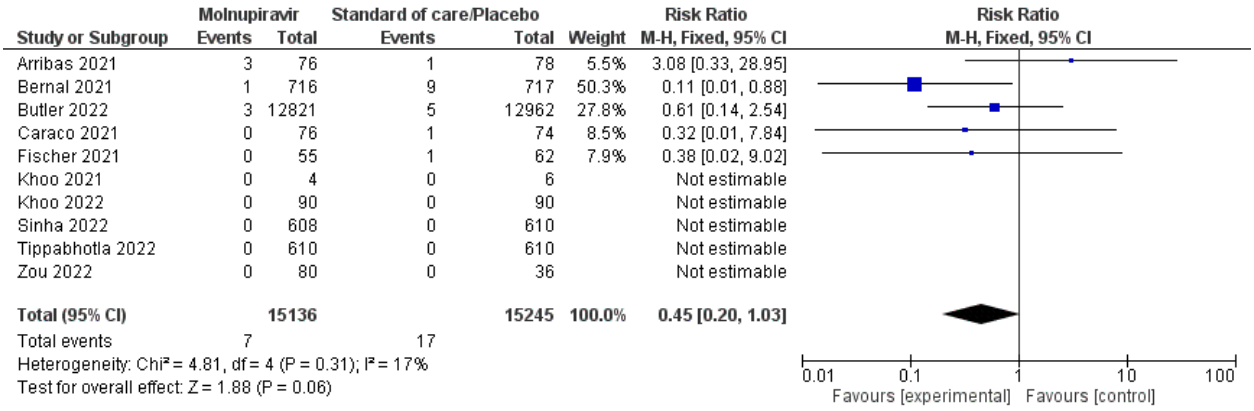


Figure 1a. All-cause mortality Day 29

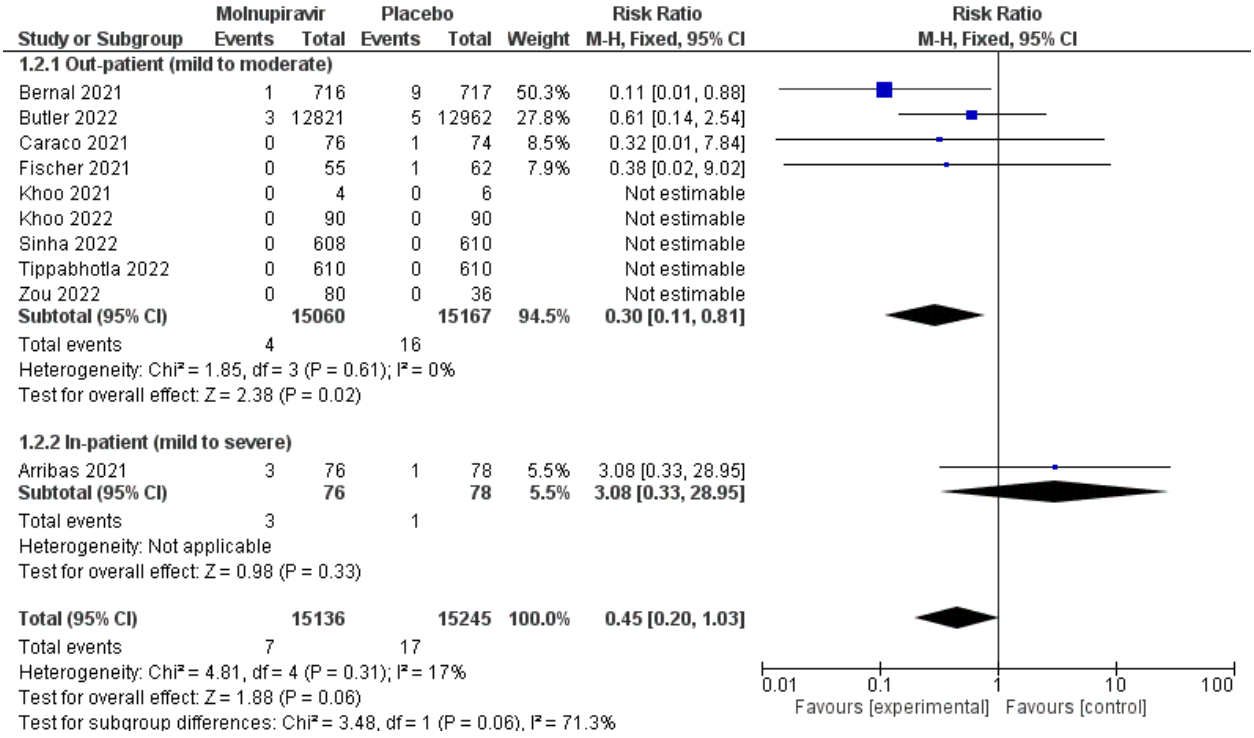


Figure 1b. Subgroup analysis on mortality based on severity

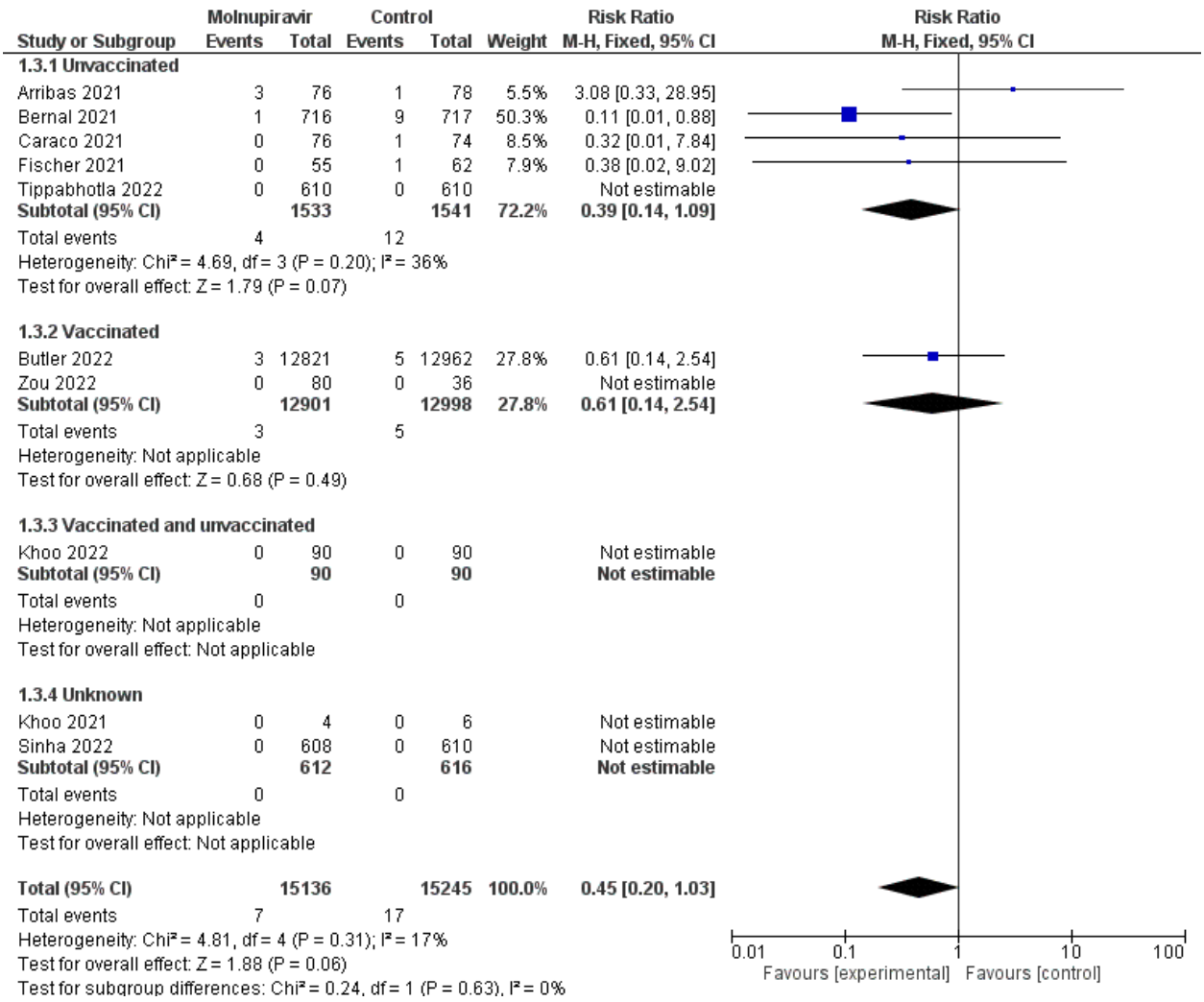


Figure 1c. Subgroup analysis on mortality based on vaccination status

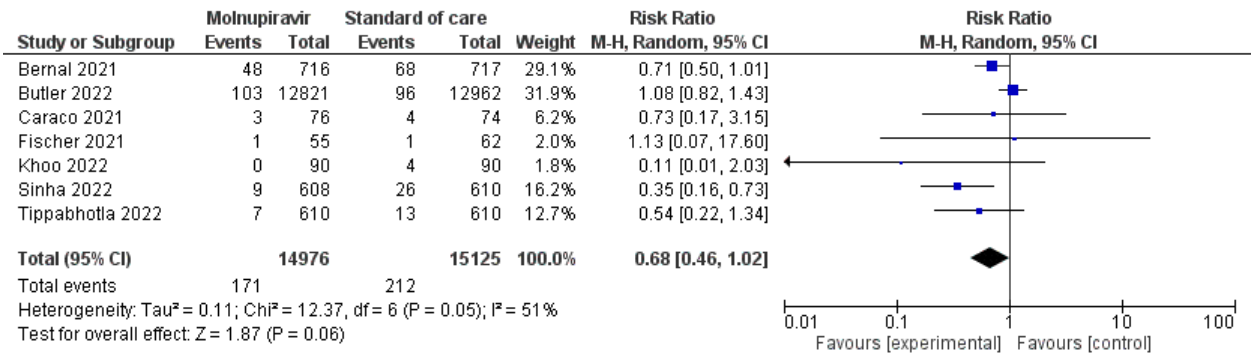


Figure 2a. Need for hospitalization (Day 29)

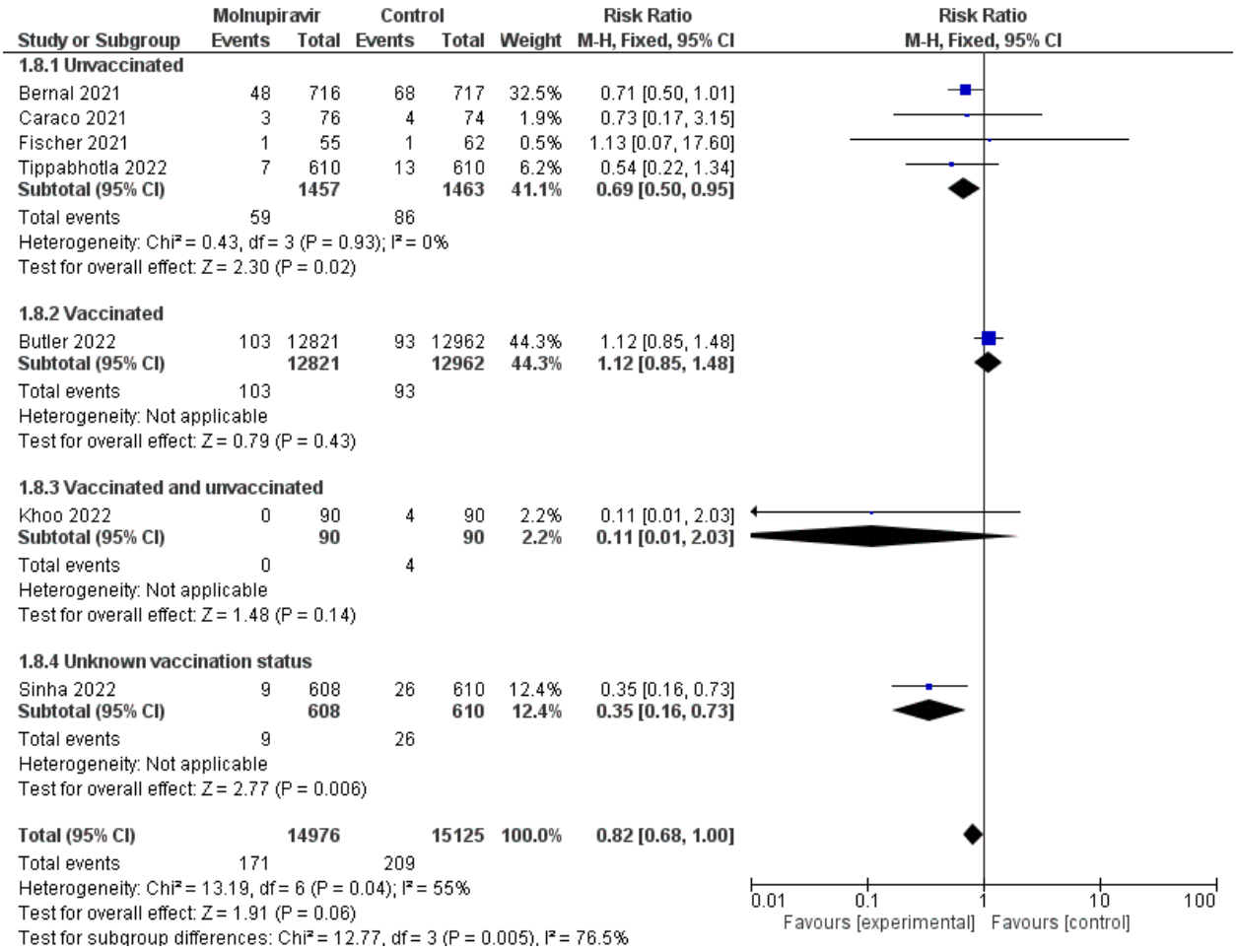


Figure 2b. Subgroup analysis on hospitalization based on vaccination status

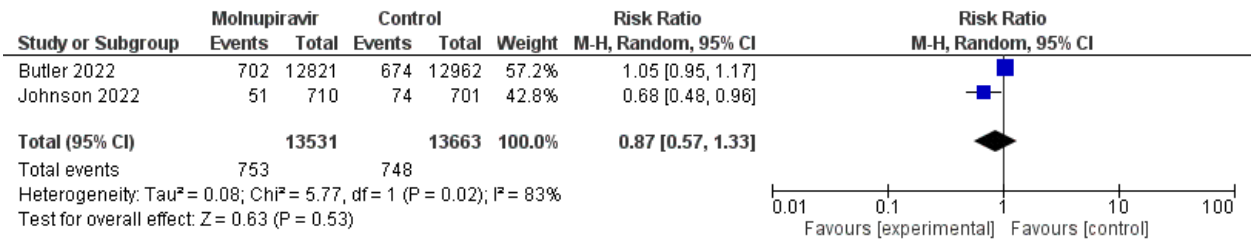


Figure 3. Emergency room visit/Acute care visit

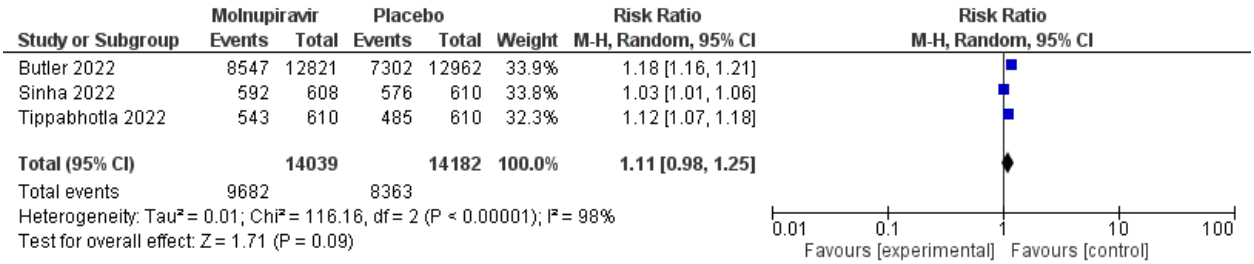


Figure 4. Clinical Improvement (Day 14 to Day 29)

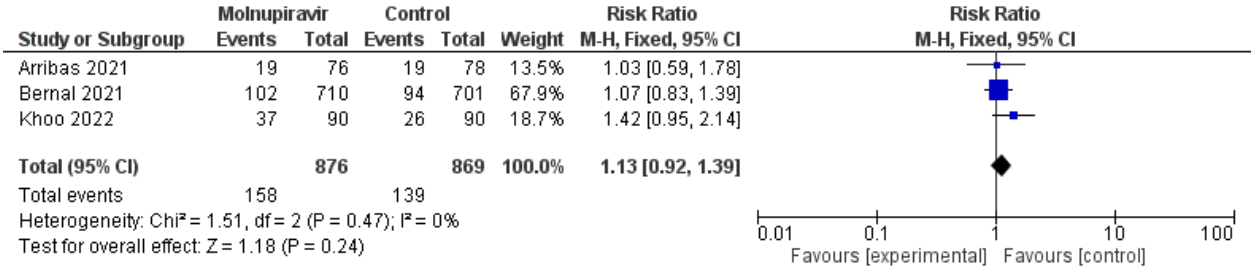


Figure 5a. WHO progression scale less than 1, Day 15

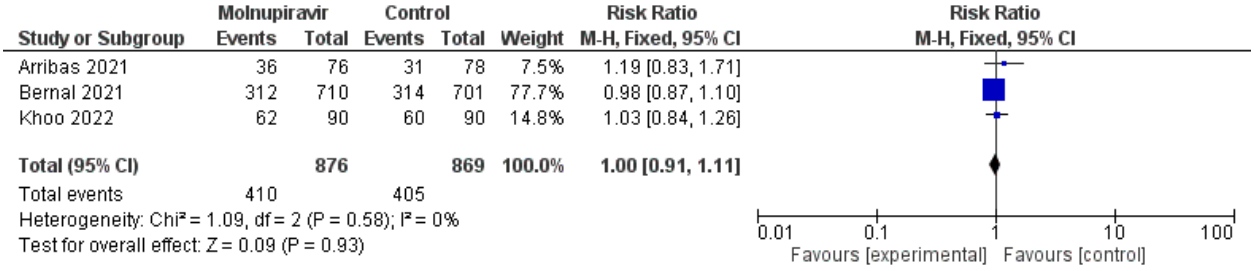


Figure 5b. WHO progression scale less than 1, Day 29

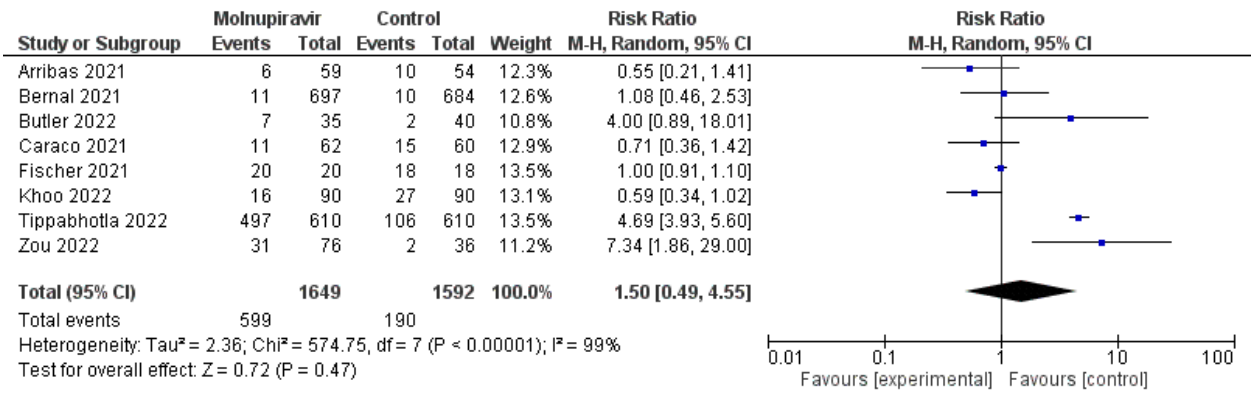


Figure 6. Viral Negative Conversion Day 7

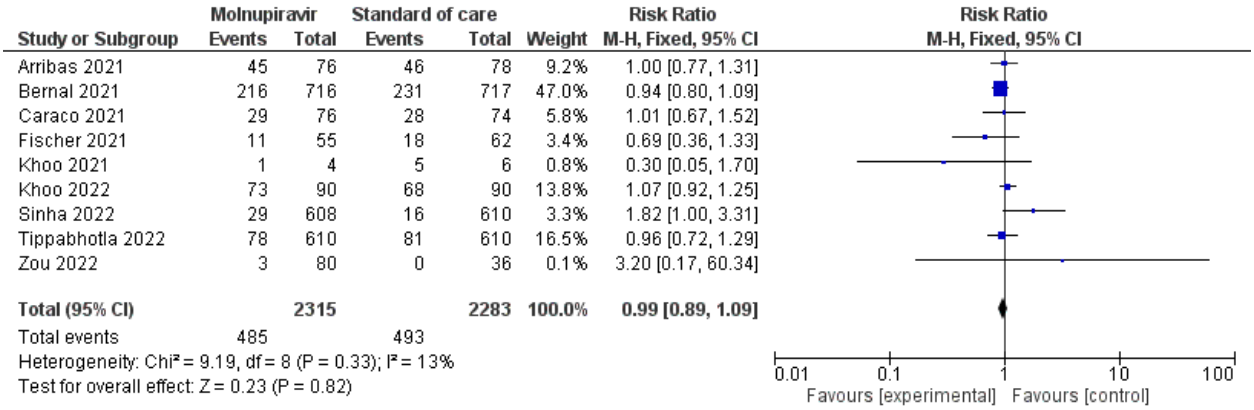


Figure 7. Adverse events

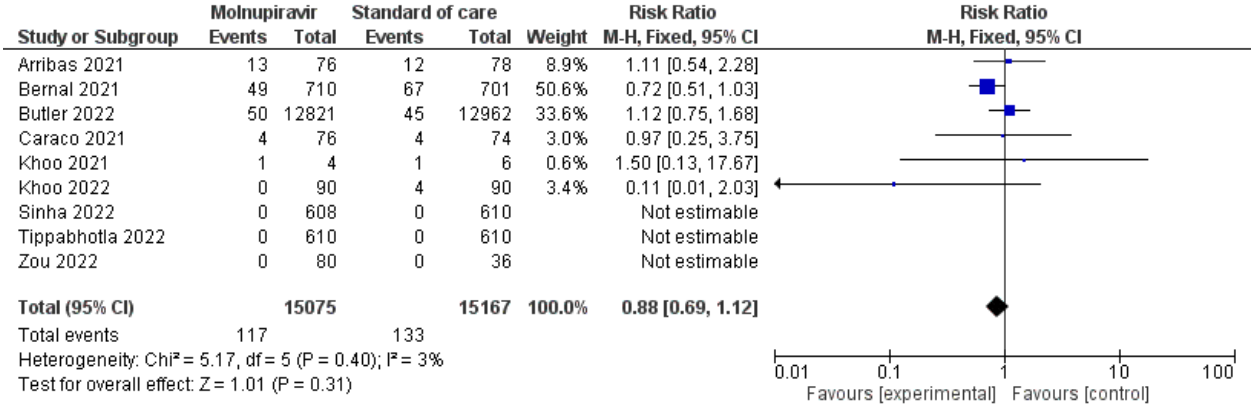


Figure 8. Serious adverse events

Appendix 7. 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 (MK-4482-013) (MOVe-AHEAD) Phase 3 Recruiting Yoshiyuki,T Merck Sharp & Dohme LLC 23 countries including the Philippines	N=1,376 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)	Percentage of participants who develop COVID-19 (up to day 14) Adverse events Discontinuation rate due to adverse events Percentage of participants who develop COVID-19 (up to day 29) RT-PCR positivity rate (up to day 14)	Double-blinded parallel randomized controlled trial
2. A multi-center, Phase-III clinical trial of Molnupiravir capsules. (NOCOV) Phase 3 Recruitment completed Singh S, et. al India	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)	Hospitalization rate (up to day 14) Hospitalization rate (up to day 28) Time to clinical improvement Mortality (day 14) RT-PCR negativity (day 10, day 15) Adverse events	Open label parallel randomized controlled trial
3. MK-4482 Ph 2/3 Study in Hospitalized Adults with COVID-19 Phase 2-3 Not Recruiting Yoshiyuki T, et. al 19 countries including the Philippines	N=1,300 Age ≥18 Confirmed COVID-19 infection (mild, moderate, or severe) Initial onset of symptoms ≤10 days prior to randomization and at least 1 sign/symptom attributable to COVID-19 present at randomization	Molnupiravir 200mg PO BID x 5 days 400mg PO BID x 5 days 800mg PO BID x 5 days Placebo (matching)	Time-to-sustained recovery (up to day 29) Adverse events Discontinuation rate due to adverse events Mortality (up to day 29) Pulmonary score WHO clinical progression scale	Double-blind randomized parallel placebo-controlled trial

Study Title	Patients (n)	Interventions	Outcomes	Method
4. 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 Phase 2/Phase 3 Open to recruitment Kumar, M et al India	N=1,282 Age 18 to 60 years old Confirmed COVID-19 infection (moderate)	Molnupiravir 800 mg PO BID Standard of care	Clinical improvement at day 14	Open label parallel comparative randomized controlled trial
5. A Phase III Clinical Trial to understand the efficacy and safety of Molnupiravir 800mg in the treatment of patients diagnosed with mild COVID-19 Phase 3 Recruitment completed Kumar, M et al India	N=1,218 N=1,282 Age 18 to 60 years old Confirmed COVID-19 infection (mild)	Molnupiravir 400 mg PO BID Standard of care	Rate of hospitalization Day 28 Clinical Improvement Time to clinical improvement All-cause mortality	Open label parallel comparative randomized controlled trial
6. The safety of Molnupiravir and its effect on viral shedding of SARS-CoV-2 (END-COVID) Phase 2 Recruitment completed Balagopal A, et all United States	N=71 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	Double-blind parallel randomized placebo-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 Phase 3 Not yet recruiting Lihiri, S et.al India	N=100 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 14Clinical improvement at Day 28	Open label parallel randomized controlled trial
8. A Clinical Study to Test the Use of Capsule Molnupiravir in Adult Patients with COVID 19 with Lung Involvement Phase 2/Phase 3 Not yet recruiting	N=1,282 Age 18-60 years old Confirmed COVID-19 patient with moderate COVID-19 disease	Molnupiravir 800mg q12 for 5 days Standard of care	Clinical improvement Adverse event Mortality Viral negative conversion	Open label parallel randomized controlled trial

Shinha S, et al India				

9. A Clinical Study to Test the Use of Capsule Molnupiravir in COVID-19 Patients with Mild Symptoms and without Lung Involvement Phase 3 Not yet recruiting Shinha S, et al India	N=1,218 Age 18-60 years old Confirmed COVID-19 patient with mild COVID-19 disease without any evidence of breathlessness	Molnupiravir 800mg q12 for 5 days Standard of care	Adverse Events Mortality Clinical Improvement Viral negative conversion	Open label parallel randomized controlled trial
10. To Evaluate the Efficacy and Safety of Molnupiravir Capsule in Treatment of Subjects with Mild Corona virus Disease (COVID-19) Phase 3 Open to recruitment Devanpally C, et al India	N=1,218 Age 18-60 years old Confirmed COVID-19 patient with mild COVID-19	Molnupiravir 800mg q12 for 5 days Standard of care	Need for hospitalization Time to clinical improvement Viral negative conversion Adverse events	Open label parallel randomized controlled trial
11. Clinical Trial to Evaluate the Efficacy and Safety of Molnupiravir Capsule in Treatment of Subjects with Moderate Coronavirus Disease (COVID-19) Phase 3 Open to recruitment Maharana A, et al India	N=1,282 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 parallel randomized controlled trial
12. 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 Phase 3 Open to Recruitment Newar S, et al India	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 Viral load timepoint Mortality Adverse events Time to clinical improvement	Open label parallel randomized controlled trial
13. A clinical study to estimate the efficacy and safety of formulation of Molnupiravir in patients with Mild COVID-19 infection. Phase 3	N=1,218 Age 18-60 years old Confirmed COVID-19 patient Mild COVID-19	Molnupiravir 800mg q12 for 5 days Standard of care	Viral negative conversion Rate of hospitalization Day 14 Adverse events Viral load timepoint All-cause mortality Time to clinical improvement	Open label parallel randomized controlled trial

Closed to recruitment of participants Krishnan, J et al India				
14. A Clinical Study with Molnupiravir Capsules 800mg in COVID-19 Patients with Mild symptoms Phase 3 Open to recruitment Douza, V et al India	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 Rate of hospitalization Day 28 Clinical Improvement All-cause mortality	Open label Parallel randomized controlled trial
15. Single and Multiple Dose Study of MK-4482 in Healthy Japanese Adults Phase 1 Recruitment completed Yoshiyuki T, et. al Japan	N=72 Age 20-60 years old previously healthy with BMI 18.5-24.9kg/m^2 Confirmed COVID-19 patients	Molnupiravir 100-1600 mg BID for 11 doses Placebo (matching)	Adverse events	Double-blinded parallel randomized placebo-controlled trial
16. A Randomised, Multi-centre, Double-blind, Phase 3 Study to Observe the Effectiveness, Safety and Tolerability of Molnupiravir Compared to Placebo Administered Orally to High-risk Adult Outpatients With Mild COVID-19 Receiving Local Standard of Care in South Africa (CoTeT) Phase 3 Recruiting Venter, FWD et. Al South Africa	N=4,000 Age >50 Non-pregnant Confirmed COVID-19 patients At least at high risk for progression to severe COVID-19	Molnupiravir 800mg BID x 5 days Placebo	Hospitalization rate Mortality day 29 Adverse events Tolerability Adherence Incidence and outcome of pregnancies	Double-blinded parallel randomized controlled trial
17. Study to evaluate the efficacy and safety of Molnupiravir capsules when administered along with Standard of Care compared to Standard of Care alone in Indian patients with mild COVID-19 disease Phase 3 Recruitment completed Lahiri S, et al India	N=1,220 Age 18-60 years old Confirmed COVID-19	Molnupiravir 800mg BID x 5 days Standard of care	Rate of hospitalization Day 14 Rate of hospitalization Day 28	Open label parallel randomized controlled trial

18. MKK4482-013: MK-4482 Phase 3 Study for Prevention of COVID-19 in Adults (MOVe AHEAD) Phase 3 Recruiting Nell Z et al South Africa and Kenya	N=150 Age >18 years old Household contact of index case At least 1 symptom attributable to COVID-19 Not confirmed or suspected COVID-19	Molnupiravir 800mg PO BID x 5 days Placebo (matching)	Percentage of participants who develop COVID-19 (up to day 14) Adverse events Discontinuation rate due to adverse events Percentage of participants who develop COVID-19 (up to day 29) RT-PCR positivity rate (up to day 14)	Doubled-blind Parallel Randomized controlled trial
19. Efficacy and safety of Thai recipes in COVID-19 patients: a pilot study Phase 2 Recruiting Potikanond,S et al Thailand	N=100 Age 20-60 years old Mild to moderate COVID-19 No history of herb allergy	Thai recipes Control: Molnupiravir 800mg BID PO x 5 days	Viral load Symptoms Serum IL-6 Liver function test Renal function test Complete blood count	Open-label Parallel randomized controlled trial
20. Evaluation of the Efficacy of Molnupiravir on Clinical and Laboratory Findings of Patients with moderate COVID-19 Phase 3 Pending Recruitment Keyvanfar, A et al Iran	N=60 Age 18 year or older Confirmed COVID-19 Moderate COVID-19 BMI <40kg/m^2	Molnupiravir 800mg BID PO x 5 days Placebo	Body temperature Rate of hospitalization O2 saturation Respiratory Rate Lymphocyte count Neutrophil count Platelet count CRP level	Double-blind parallel randomized placebo controlled trial
21. Comparing the efficacy of Molnupiravir and placebo on recovery rate in patients with mild COVID-19, a randomized multicenter clinical trial Phase 2-3 Recruiting Soleymanitabar, A et al Iran	N=500 Age 18 years and older Living in a family with at least one infected person with COVID-19 Not having pulmonary involvement COVID-19 confirmed O2 sat >93%	Molnupiravir 200mg PO for 5 days with Diphenhydramine syrup, vitamin C, vitamin D, famotidine Control: Diphenhydramine syrup, vitamin C, vitamin D, famotidine	Blood pressure Dry cough existence Dyspnea Fever Muscular pain Viral negative conversion Pulse rate Respiratory rate CRP level ESR level O2 saturation	Double-blind parallel randomized placebo controlled trial
22. Randomised Evaluation of COVID-19 Therapy (RECOVERY) Phase 2/3 Recruiting Horby P, et al 8 countries	N=50,000 Age: 0 years and older Hospitalized Viral pneumonia syndrome COVID-19 confirmed	Molnupiravir 800mg BIC x 5 days Lopinavir-Ritonavir Corticosteroid Hydroxychloroquine Azithromycin Convalescent plasma Tocilizumab Immunoglobulins Synthetic neutralizing antibodies Aspirin Colchicine Baricitinib Anakinra Dimethyl fumarate High Dose Corticosteroid Empagliflozin Sotrovimab Paxlovid	All-cause mortality Duration of hospital stay (Day 28) Death or need for mechanical ventilation or ECMO	Open label factorial assignment randomized controlled trial

		Standard of Care		
23. AGILE CST2: Seamless Phase I/IIa Platform for the Rapid Evaluation of Candidates for COVID-19 Treatment Phase 1/2 Recruiting Khoo, S et al South Africa and UK	N=600 Age 18 years and older Mild, Moderate, Severe COVID-19	Molnupiravir BID x 5 days Standard of care	Adverse events Time to clinical Improvement Safety and tolerability of multiple ascending doses Hospitalization O2 reduction	Open label sequential assignment randomized control
24. Finding Treatments for COVID-19: A Trial of Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV) Phase 2 Recruiting Schilling W, et al Brazil and Thailand	N=1,500 Age 18-50 years old Early symptomatic COVID-19 <4 days O2 sat >96%	Molnupiravir 800mg BID x 5-7 days Casirivimab/Imdevimab Favipiravir Ivermectin Remdesivir Fluoxetine Nirmatrelvir/ritonavir Nitazoxanide Standard of care	Viral clearance Day 7 Viral level in early COVID-19 disease Day 7 Rate of hospitalization	Open label parallel randomized controlled trial