Virology and Safety profile of Molnupiravir at three different doses: A systematic review and Meta-analysis

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Abstract

Molnupiravir (also known as EIDD-2801/MK-4482), which is used as an antiviral drug has its mechanism of action by incorporating into the viral genome increasing errors, mismatching, and misdirecting the viral polymerase, leading to the accumulation of deleterious errors and halting viral RNA replication of SARS-CoV-2 and other RNA viruses. Our meta-analysis aims to evaluate virology profile, and adverse effects associated with the use of molnupiravir on a large patient population. Following PRISMA guidelines performed a thorough literature search of electronic and medical databases (MEDLINE and Cochrane CENTRAL) from their establishment to January 2023 without any limitations on time, language, or sample size. The random effects model was utilized to calculate the weighted mean difference (WMD) and its associated 95% confidence intervals (CIs) to pool continuous outcomes of interest. Using a random effects model, odds ratio, and accompanying 95% confidence intervals (CIs). Molnupiravir 800 mg at day 5 is significant in creating viral RNA error rate (WMD: 4.91; 95% CI; [1.19, 8.63] p=0.01; I ^{2}=0%). (P-value for subgroup differences = 0.05). A significant outcome was reported with 400mg molnupiravir (WMD: 2.27; 95% CI; 2.27 [0.50, 4.65] p=0.02; I ^{2}=0%). Significant outcome for mean change in SARS-COV-2 RNA viral load from baseline in nasopharyngeal sample at 800 mg molnupiravir on day 3 (WMD: -0.22; 95% CI; [-0.35,-0.08] p=0.002; I ^{2}=0%), day 5 (WMD: -0.32; 95% CI; [-0.53,-0.11] p=0.003; I ^{2}=24%) and overall pooled analysis (WMD: -0.17; 95% CI; [-0.29, 0.33] p=0.003; I ^{2}=32%). Similarly for 400 mg at DAY 5 and overall analysis comparing the molnupiravir group to the placebo group, a significant reduction in viral RNA load was seen from baseline. (WMD: -0.46; 95% CI; [-0.77,-0.15] p=0.004; I ^{2}=0%), (WMD: -0.28; 95% CI; [-0.49,-0.07] p=0.009; I ^{2}=0%). Molnupiravir 400mg significantly reduced the incidence of death as compared to the placebo group. (RR: 0.17; 95% CI; [0.07, 0.43] p=0.0002; I ^{2}=0%). In our meta-analysis, we conclude that molnupiravir is effective in treating SARS-COV-2 patients with respect to eliminating the virus from the host through their mechanism of action. Thereby, widely used and appropriate to treat SARS-COV-2.

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Abstract:

Molnupiravir (also known as EIDD-2801/MK-4482), which is used as an antiviral drug has its mechanism of action by incorporating into the viral genome increasing errors, mismatching, and misdirecting the viral polymerase, leading to the accumulation of deleterious errors and halting viral RNA replication of SARS-CoV-2 and other RNA viruses. Our meta-analysis aims to evaluate virology profile, and adverse effects associated with the use of molnupiravir on a large patient population. Following PRISMA guidelines performed a thorough literature search of electronic and medical databases (MEDLINE and Cochrane CENTRAL) from their establishment to January 2023 without any limitations on time, language, or sample size. The random effects model was utilized to calculate the weighted mean difference (WMD) and its associated 95% confidence intervals (CIs) to pool continuous outcomes of interest. Using a random effects model, odds ratio, and accompanying 95% confidence intervals (CIs). Molnupiravir 800 mg at day 5 is significant in creating viral RNA error rate (WMD: 4.91; 95% CI; [1.19, 8.63] p=0.01; I^2=0%). (P-value for subgroup differences = 0.05). A significant outcome was reported with 400mg molnupiravir (WMD: 2.27; 95% CI; 2.27 [0.50, 4.65] p=0.02; I^2=0%). Significant outcome for mean change in SARS-COV-2 RNA viral load from baseline in nasopharyngeal sample at 800 mg molnupiravir on day 3 (WMD: -0.22; 95% CI; [-0.35,-0.08] p=0.002; I^2=0%), day 5 (WMD: -0.32; 95% CI; [-0.53,-0.11] p=0.003; I^2=24%) and overall pooled analysis (WMD: -0.17; 95% CI; [-0.29, 0.33] p=0.003; I^2=32%). Similarly for 400 mg at DAY 5 and overall analysis comparing the molnupiravir group to the placebo group, a significant reduction in viral RNA load was seen from baseline. (WMD: -0.46; 95% CI; [-0.77,-0.15] p=0.004; I^2=0%), (WMD: -0.28; 95% CI; [-0.49,-0.07] p=0.009; I^2=0%). Molnupiravir 400mg significantly reduced the incidence of death as compared to the placebo group. (RR: 0.17; 95% CI; [0.07, 0.43] p=0.0002; I^2=0%). In our meta-analysis, we conclude that molnupiravir is effective in treating SARS-COV-2 patients with respect to eliminating the virus from the host through their mechanism of action. Thereby, widely used and appropriate to treat SARS-COV-2.

INTRODUCTION

Coronavirus disease (COVID-19) which is defined as a severe acute respiratory syndrome caused by a coronavirus, and hence also known as SARS-CoV-2 has created a devastating situation, infecting 610 million people along with 6.5 million deaths worldwide. [1]

Since the virus has a rapidly mutating property, many new variants have emerged increasing infectivity and transmission. The Omicron variant that is currently dominating has a higher infectivity and strong vaccine breakthrough ability and among the three lineages (BA.1, BA.2, BA.3) of this variant, BA.2 has become a "variant of concern" increasing hospitalization. [2,3]

Although many patients recover without treatment, a significant number of patients infected with COVID-19 need hospitalization, especially the ones with pre-existing conditions such as diabetes mellitus, obesity, and cardiac conditions. Although the administration of vaccines and various techniques are effective in reducing the incidence of hospitalization and death, its coverage remains insufficient. [4,5,6]

The need for initiation of treatment is required at the earliest after the onset of symptoms, and therapies that can be easily administered by patients are needed since no therapies have been shown to eliminate the infectious virus and prevent transmission, oral antivirals are needed. There are two classes of antiviral drugs authorized for COVID-19 treatment; remdesivir and monoclonal antibodies. Remedesivir is approved by the FDA for the treatment of severe COVID-19 patients hospitalized. [7] Molnupiravir (also known as EIDD-2801/MK-4482), which is used as an antiviral drug is an orally administered, small molecule ribonucleoside

prodrug of N-hydroxycytidine that is rapidly metabolized by esterases and absorbed into the system and acts by phosphorylating into NHC-triphosphate intracellularly, incorporating into the viral genome increasing errors, mismatch and misdirects the viral polymerase, leading to accumulation of deleterious errors and halting viral RNA replication of SARS-CoV-2 and other RNA viruses. [4,6,8]

In the first 5 days of infections, when the patient is characterized by an early peak viral load, any antiviral administered early can have the most effect on the infection. Molnupiravir has three doses for administration (200mg, 400mg, and 800mg) that significantly reduce viral titers and block transmission to uninfected people. Studies have shown that molnupiravir administered in PCR-positive patients in aforementioned doses twice daily for 5 days, was found negatively cultured in all the patients after administration of the drug compared to placebo. [8] Molnupiravir was found well tolerated and has a shred of strong evidence that it is not mutagenic or genotoxic in mammals even at exposure above therapeutic targets, however, it has several adverse effects which can be mild-severe. [6,9] Our meta-analysis aims to evaluate virology profile, and adverse effects associated with the use of molnupiravir on a large patient population.

METHODS:

This systematic review and meta-analysis was conducted in accordance with the structure laid out by the Cochrane collaboration and followed the Preferred Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[10,11] No ethical approval required and this study was registered on PROSPERO, The International Prospective Register of Systematic Reviews. (CRD42023396922).

Data Sources and Search Strategy:

Two independent authors MS and SO performed a thorough literature search of electronic and medical databases (MEDLINE and Cochrane CENTRAL) from their establishment to January 2023 without any limitations on time, language, or sample size. Both entry terms and MeSH (Medical Subject Headings) terms were used as search terms. Supplementary Table S1 provides a detailed description of the search approach employed in each of the databases. For each search engine, the query has been modified and reoriented as necessary. The bibliographies of pertinent review articles, internet databases like clinicaltrials.gov, and preprint sites like medrvix were also checked for grey literature.

Study Selection:

The EndNote Reference Manager (Version X7.5; Clarivate Analytics, Philadelphia, Pennsylvania) was used to find and eliminate duplicate articles after transferring the articles found by the systematic search. Two independent reviewers (MS and SO) carefully examined the titles and abstracts of the remaining publications before thoroughly going over the whole text to confirm relevance. Discussion was used to settle any disagreements. Studies were chosen if they matched the predetermined qualifying requirements listed below : (a) Covid-19 patients on molnupiravir therapy (b) Patients above the age of 18 years (c) Patients taking 800mg, 400mg, and 200 mg molnupiravir.(d) Clinical trials (randomised controlled trial) Studies that included patients aged < 18, patients with 50mg, 300mg, and 600mg of molnupiravir were excluded since a few studies have enrolled the patient on the aforementioned dosage of molnupiravir. Combination therapy was excluded as well. Duplicate records, case reports, commentaries, and editorials were also excluded.

Data Extraction, quality assessment and risk of bias

Data on study year, study design, sample size, place, age, gender, primary and secondary outcome were extracted on a standard excel sheet from the eligible articles. The primary outcomes of interest were(1) SARS-COV-2 RNA error rate. (2) Time for clearance SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample. (3) Mean change in SARS-COV-2 from baseline in nasopharyngeal sample. The secondary outcomes of interest are 20 adverse events which include any AEs, serious AEs, investigations, cardiac disorders, blood and lymphatic disorders, general administration site disorders, GI disorders, respiratory AE, renal AE, vascular AE, skin AE, nervous system AE, psych AE, MSK AE, eye AE, injury and poisoning, infection and infestation, metabolism and nutrition, drug discontinuation and death,

Cochrane Collaboration's risk of bias 2.0 (ROB 2.0) tool was used to assess the risk of bias in RCTs across five domains (randomization, intended intervention, missing data, outcome measurement, and reported results) [12]. Data extraction and quality assessment was carried out by two researchers (MS and SO) independently and any discrepancies were resolved after discussion.

The quality of evidence was graded as very low, low, moderate, or high using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) assessment tool on the basis of risk of bias, publication bias, imprecision, inconsistency, and indirectness.

Statistical Analysis

The statistical analysis was performed using Review Manager Version 5.4 Cochrane Collaboration. Random effects model was utilised to calculate the weighted mean difference (WMD) and its associated 95% confidence intervals (CIs) in order to pool continuous outcomes of interest. Using a random effects model, odds ratio and accompanying 95% confidence intervals (CIs). were integrated for the dichotomous outcome. For adverse events, data was used to calculate risk ratios (RRs) and 95% confidence intervals, which were then meta analysed using a random effects model. For each outcome, the results were displayed as forest plots. Sensitivity analysis was used to examine the impact of each study on the pooled estimate for outcomes where studies showed a high level of heterogeneity. Following the Cochrane Guidelines, no funnel plots were built to test for publication bias because the number of papers pooled for all outcomes was fewer than 10. The aggregated studies' heterogeneity was quantified using Higgins I2 statistics. [13] A value of I2 = 25–50% was deemed mild, 50–75% as moderate, and >75% as severe heterogeneity. Every time, a p-value of 0.05 or less was deemed significant.

RESULTS:

Study selection and characteristics:

The PRISMA flow chart provides an overview of the study selection process and search strategy (Figure1). During the search, 332 appropriate studies were discovered. After screening, 7 studies were ultimately picked for the analysis. The studies that were included were all RCTS. 2369 adults made up the entire study population in this meta-analysis, with 968 people in the control group and 1401 people in the molnupiravir group. The baseline parameters and other information for the included studies are displayed in Table 1.

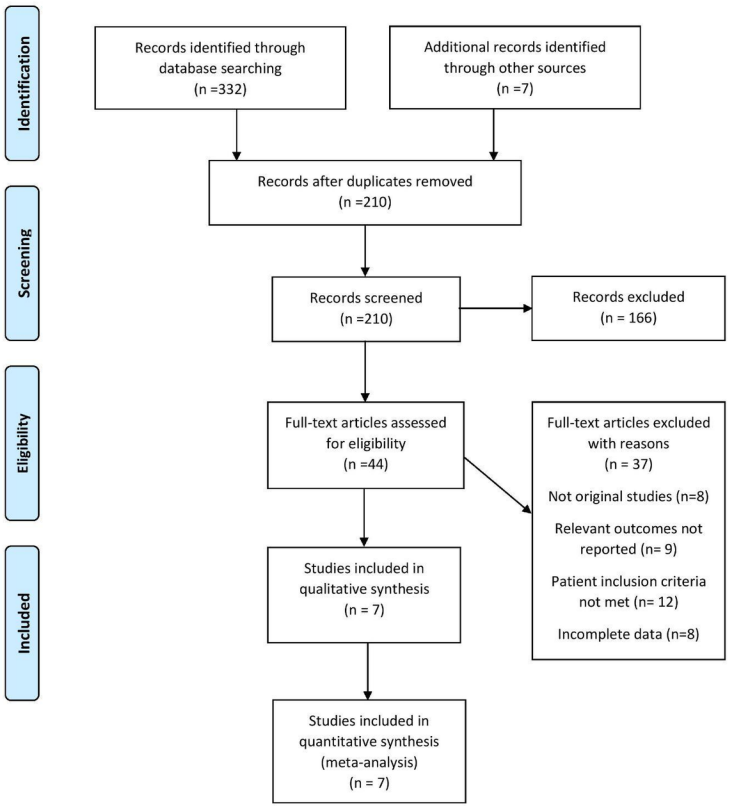

Figure 1 - PRISMA Flow Diagram:

Quality Assessment:

5 of the 7 studies included in our meta-analysis had a low risk of bias. All domains reported a low risk for the RCTs as the procedure, analysis, and outcomes were adequate in these studies. The study by Zou et al had a moderate risk of bias due to some concerns in the randomization process while the study by Kho et al., had a high risk of bias due to serious issues in the randomization process. Detailed tables of Quality and Risk of Bias Assessment results are presented in the supplementary document.

GRADE

Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] Outcome	Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] Outcome	Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] Outcome	Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] No. of participants (studies)	Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] No. of participants (studies)	Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] Effect estimate (95% CI)	Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] Risk of bias	Arribas [14], Caraco[6], Bernal[4], Khoo[8], Zou[3] Risk of bias	800 mg Inconsistency	800 mg Inconsistency	800 mg Inconsistency	800 mg Indirectness	800 mg Indirectness	800 mg Imp
A.Virology Profile 1.SARS-COV-2 RNA ERROR RATE	A.Virology Profile 1.SARS-COV-2 RNA ERROR RATE	A.Virology Profile 1.SARS-COV-2 RNA ERROR RATE	145	145	MD 1.71 [-0.11, 3.53]	Low	Low	Moderate	Moderate	Moderate	Not Serious	Not Serious	Seric
2. Time for clearance SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample	2. Time for clearance SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample	2. Time for clearance SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample	775	775	OR 1.90 [0.80, 4.53]	Low	Low	Moderate	Moderate	Moderate	Not Serious	Not Serious	Seric

3. Mean change in SARS-COV-2 from baseline in nasopharyngeal sample	**3. Mean change in SARS-COV-2 from baseline in nasopharyngeal sample**	**3. Mean change in SARS-COV-2 from baseline in nasopharyngeal sample**	4534	4534	MD -0.17 [-0.29, -0.06]	Low	Low	Mild	Mild	Mild	Not Serious	Not Serious	Not Seric
B. Mortality	**B. Mortality**	**B. Mortality**	1823	1823	RR 0.48 [0.12, 1.98]	Low	Low	Mild	Mild	Mild	Not Serious	Not Serious	Seric
Arribas[41], Caraco[42], Outcome	**Arribas[41], Caraco[42], Outcome**	**Arribas[41], Caraco[42], No. of participants (studies)**	**Arribas[41], Caraco[42], No. of participants (studies)**	**Arribas[41], Caraco[42], Effect estimate (95% CI)**	**Arribas[41], Caraco[42], Effect estimate (95% CI)**	**Arribas[41], Caraco[42], Effect estimate (95% CI)**	**Arribas[41], Caraco[42], Risk of bias**	**Arribas[41], Caraco[42], Risk of bias**	**Arribas[41], Caraco[42], Inconsistency**	**Arribas[41], Caraco[42], Inconsistency**	**Arribas[41], Caraco[42], Indirectness**	**Arribas[41], Caraco[42], Indirectness**	**Arribas[41], Caraco[42], Indirectness**
A.Virological Profile 1.**SARS-COV-2 RNA ERROR RATE**	A.Virological Profile 1.**SARS-COV-2 RNA ERROR RATE**	161	161	MD 2.57 [0.50, 4.65]	MD 2.57 [0.50, 4.65]	MD 2.57 [0.50, 4.65]	Low	Low	Low	Low	Low	Not Serious	Not Seric

2. Time for clearance SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample	**2. Time for clearance SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample**	657	657	OD 0.81 [0.45, 1.45]	OD 0.81 [0.45, 1.45]	OD 0.81 [0.45, 1.45]	Low	Low	Mild	Mild	Mild	Not Serious	Not Serio
3. Mean change in SARS-COV-2 from baseline in nasopharyngeal sample	**3. Mean change in SARS-COV-2 from baseline in nasopharyngeal sample**	466	466	MD -0.28 [-0.49, -0.07]	MD -0.28 [-0.49, -0.07]	MD -0.28 [-0.49, -0.07]	Low	Low	Low	Low	Low	Not Serious	Not Serio
B. Mortality	**B. Mortality**	423	423	RR 0.17 [0.07, 0.43]	RR 0.17 [0.07, 0.43]	RR 0.17 [0.07, 0.43]	Low	Low	Low	Low	Low	Not Serious	Not Serio

Arribas[14], Caraco[6], Fischer[7], Painter[9]	**Arribas[14], Caraco[6], Fischer[7], Painter[9]**	**Arribas[14], Caraco[6], Fischer[7], Painter[9]**	**Arribas[14], Caraco[6], Fischer[7], Painter[9]**	**200 mg**	**200 mg**	**200 mg**	**200 mg**

Outcome	No. of participants (studies)	Effect estimate (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias
A.Virological Profile 1.**SARS-COV-2 RNA ERROR RATE**	150	MD 1.27 [-0.32, 2.86]	Low	Low	Not Serious	Serious	N/A
2. Time for clearance SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample	590	OD 1.33 [0.80, 2.20	Low	Low	Not Serious	Serious	N/A
3. Mean change in SARS-COV-2 from baseline in nasopharyngeal sample	382	MD -0.07 [-0.32, 0.17]	Low	Low	Not Serious	Not Serious	N/A
B. Mortality	381	RR 1.74 [0.48, 6.30]	Low	Low	Not Serious	Serious	N/A

Virology profile

SARS COV-2 RNA error rate

At 800 mg molnupiravir:

DAY 3:

No significant difference was observed in the SARS COV-2 RNA error rate between the molnupiravir group compared to the control group. (WMD: 1.04; 95% CI; [-0.18, 2.26] p=0.09; I^2=22%). (Fig 2A)

DAY 5:

Significant difference was observed in the SARS COV-2 RNA error rate between the molnupiravir group compared to the placebo group. (WMD: 4.91; 95% CI; [1.19, 8.63] p=0.01; I^2=0%). *(P-value for subgroup differences = 0.05).* (Fig 2A)

Overall: No significant difference observed in either interventional groups, (WMD: 1.71; 95% CI; [-0.11, 3.53] p=0.07; I^2=49%).

At 400 mg molnupiravir:

DAY 3:

Molnupiravir group had no significant difference in the SARS COV-2 RNA error rate compared to the placebo arm (WMD: 3.28; 95% CI; [-0.42, 6.97] p=0.08; I^2=0%). (Fig 2B)

DAY 5:

Molnupiravir group had no significant difference in the SARS COV-2 RNA error rate compared to the placebo arm (WMD: 2.53; 95% CI; [-1.04, 6.10] p=0.17; I^2=46%). (Fig 2B)

Overall: A significant outcome reported with 400mg molnupiravir (WMD: 2.27; 95% CI; 2.27 [0.50, 4.65] p=0.02; I^2=0%).

At 200 mg molnupiravir:

DAY 3:

Comparing the Molnupiravir group to the placebo group, there was no discernible change in the SARS COV-2 RNA error rate. (WMD: 1.00; 95% CI; [-1.40, 3.40] p=0.41; I^2=22%) (Fig 2C)

DAY 5:

Comparing the Molnupiravir group to the placebo group, there was no significant change in the SARS COV-2 RNA error rate. (WMD: 2.58; 95% CI; [-0.44, 5.60] p=0.09; I^2=0%) (Fig 2C)

Overall: No significant results obtained in overall pooled analysis of molnupiravir 200mg dose. (WMD: 1.27; 95% CI; [-0.32, 2.86] p=0.12; I^2=6%) (Fig 2C)

Figure 3: Time for clearance of SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample

At 800 mg molnupiravir:

DAY 3:

Comparing the Molnupiravir group to the placebo group, there was no discernible change in the time for clearance of SARS-COV-2 (WMD: 1.94; 95% CI; [0.29, 12.80] p=0.49; I^2=66%) (Fig 3A)

DAY 5:

Comparing the Molnupiravir group to the placebo group, there was no discernible change in the time for clearance of SARS-COV-2 (WMD: 3.73; 95% CI; [0.22, 62.75] p=0.36; I^2=79%) (Fig 3A)

DAY 29:

There was no noticeable difference between the Molnupiravir group and the placebo group in the amount of time it took for SARS-COV-2 to clear. (WMD: 1.72; 95% CI; [0.65, 4.53] p=0.27; I^2=36%) *(P-value for subgroup differences = 0.88).* (Fig 3A).

Overall: The pooled analysis of 800mg molnipiravir and placebo deduce insignificant outcome in overall efficacy, (WMD: 1.90; 95% CI; [0.80, 4.53] p=0.14; I^2=57%)

At 400 mg molnupiravir:

DAY 3:

There was no noticeable difference in SARS-COV-2 clearance time between the Molnupiravir group and the placebo group. (WMD: 0.77; 95% CI; [0.13,4.48] p=0.77; I^2=53%) (Fig 3B)

DAY 5:

There was no noticeable difference in SARS-COV-2 clearance time between the Molnupiravir group and the placebo group. (WMD: 1.82; 95% CI; [0.07, 44.46] p=0.71; I^2=77%) (Fig 3B)

DAY 29:

There was no noticeable difference in SARS-COV-2 clearance time between the Molnupiravir group and the placebo group. (WMD: 0.74; 95% CI; [0.39, 3.14] p=0.62; I^2=0%) *(P-value for subgroup differences = 0.87).* (Fig 3B)

Overall: No significant outcome observed for pooled analysis of 400mg dose of molnupiravir (WMD: 0.81; 95% CI; [0.45, 1.45] p=0.45; I^2=026%).

At 200 mg molnupiravir:

DAY 3:

The amount of time it took SARS-COV-2 to clear did not differ significantly between the Molnupiravir group and the placebo group. (WMD: 1.26; 95% CI; [0.51,1.41] p=0.36; I^2=0%) (Fig 3C)

DAY 5:

The amount of time it took SARS-COV-2 to clear did not differ significantly between the Molnupiravir group and the placebo group.(WMD: 1.14; 95% CI; [0.48,2.67] p=0.77; I^2=0%) (Fig 3C)

DAY 29:

The amount of time it took SARS-COV-2 to clear did not differ significantly between the Molnupiravir group and the placebo group. (WMD: 1.62; 95% CI; [0.69,3.80] p=0.27; I^2=0%) *(P-value for subgroup differences = 0.84).* (Fig 3C)

Overall: No significant outcome reported in pooled analysis of molnupiravir 200 mg dose (WMD: 1.33; 95% CI; [0.80, 2.20] p=0.27; I^2=0%).

Figure 4: Mean change in SARS-COV-2 RNA viral load from baseline in nasopharyngeal sample:

At 800 mg molnupiravir:

DAY 3:

Significant reduction in viral RNA load from baseline in the molnupiravir group compared to placebo group (WMD: -0.22; 95% CI; [-0.35,-0.08] p=0.002; I^2=0%) (Fig 4A)

DAY 5:

Compared to the placebo group, there was a significant drop in the viral RNA burden in the molnupiravir group from baseline. (WMD: -0.32; 95% CI; [-0.53,-0.11] p=0.003; I^2=24%) (Fig S8)

DAY 10:

No significant reduction in viral RNA load from baseline in the molnupiravir group compared to placebo group (WMD: -0.17; 95% CI; [-0.37,-0.04] p=0.11; I^2=0%) (Fig 4A)

DAY 29:

Compared to the placebo group, there was no significant drop in the viral RNA burden in the molnupiravir group from baseline. (WMD: 0.11; 95% CI; [-0.12, 0.33] p=0.36; I^2=0%) *(P-value for subgroup differences = 0.04).* (Fig 4A)

Overall: The overall pooled analysis of molnupiravir 800mg for mean change in SARS-COV-2 in nasopharyngeal sample from baseline deduce a significant outcome in favour of the interventional drug (WMD: -0.17; 95% CI; [-0.29, 0.33] p=0.003; I^2=32%).

At 400 mg molnupiravir:

DAY 3:

Comparing the molnupiravir group to the placebo group, no significant reduction in viral RNA load was seen from baseline. (WMD: -0.13; 95% CI; [-0.41, 0.16] p=0.38; I^2=0%) (Fig 4B)

DAY 5:

Comparing the molnupiravir group to the placebo group, a significant reduction in viral RNA load was seen from baseline. (WMD: -0.46; 95% CI; [-0.77,-0.15] p=0.004; I^2=0%) (Fig 4B)

Overall: The pooled analysis of molnupiravir 400mg shows significant outcome for the result (WMD: -0.28; 95% CI; [-0.49,-0.07] p=0.009; I^2=0%) (Fig 4C)

At 200 mg molnupiravir:

DAY 3:

Compared to the placebo group, there was a significant drop in the viral RNA burden in the molnupiravir group from baseline. (WMD: -0.05; 95% CI; [-0.39, 0.28] p=0.76; I^2=0%) (Fig 4C)

DAY 5:

Compared to the placebo group, there was a significant drop in the viral RNA burden in the molnupiravir group from baseline. (WMD: -0.09; 95% CI; [-0.45,-0.26] p=0.60; I^2=0%) (Fig 4C)

Overall: The pooled analysis of 200mg molnupiavir compared with placebo explicit no significance (WMD: -0.07; 95% CI; [-0.31,0.17] p=0.56; I^2=0%) (Fig 4C)

Adverse events: Results on Adverse events are provided in supplementary document 2.0.

Discussion In this meta-analysis, we evaluate the safety and virology profile of molnupiravir at three dosages (800mg, 400mg, and 200mg) in Covid-19 positive patients. Our combined analysis of seven RCTs, comprising 2369 adult patients in total demonstrates that no particular dose of molnupiravir has a statistically significant effect on all three efficacy parameters (namely SARS-CoV-2 viral RNA error rate, time for clearance of SARS-CoV-2 RNA from nasopharyngeal sample, and mean change in SARS-CoV-2 RNA from nasopharyngeal sample from baseline). Moreover, compared with a placebo, molnupiravir was not associated with an increased risk of other adverse events. However, the drug manifests a decrease in the rate of deaths in patients receiving 400mg of molnupiravir.

To our knowledge, this is the first meta-analysis focusing on the Virology and safety profile of molnupiravir alone. Prior to our study, two network meta-analyses; one by Pitre T et.al [15], the other by Lai et.al. [16], and one meta-analysis by Wen W et.al [17] was conducted. However, all of these studies assessed the safety and efficacy of molnupuravir in addition to other antiviral agents and none of these studies accounted for the dosage of molnupuravir.

With regards to the efficacy of molnupiravir against SARS-CoV-2, our analysis demonstrates that when compared with the placebo, 800 mg molnupiravir had the highest SARS-COV2 RNA error rate on day 5, end of treatment (EOT). Furthermore, a significant reduction in mean change in SARS-Cov-2 from baseline in nasopharyngeal swabs was also observed on day 3 and day 5 with 800mg and overall efficacy with 400mg. Consistent with the mode of action of molnupiravir. Fischer et al. concluded that the least squares mean viral load change from baseline was substantially higher for patients who received 400 or 800 mg of molnupiravir on day 5 when compared to the placebo group, with differences in the least squares means of 0.434 and 0.547 log10 copies/ml (P = 0.030 and 0.006, respectively). It was also noticed that when patients taking 800 mg

of molnupiravir were compared to those taking a placebo, infectious virus isolation dropped significantly on Day 3 (1.9% vs. 16.7%; P=0.016). Moreover, no viruses were isolated from participants who received 400 or 800 mg of molnupiravir, compared with 11.1% (6/54) of those who got a placebo (p=0.03), infectious viral isolation decreased on Day 5 after molnupiravir treatment. *[7]*

After it enters the host cell, molnupiravir is converted into its active form (NHC-triphosphate) which is then used as a substrate for RNA replication by the pathogen's RNA-dependent RNA polymerase (RdRp). NHC- triphosphate exists in two tautomeric forms and can thus act as Cytosine (C) or Uracil (U). [18] Normally, Adenine (A) binds with Uracil (U) and Guanine (G) pairs with Cytosine (C). However, with molnupiravir, the viral RdRp incorporates NHC-triphosphate with G and A respectively. One important property of NHC-triphosphate is that it does not halt the extension of the antisense viral RNA. When this negative (-) RNA strand with NHC-triphosphate is used as a positive (+) template for progeny RNA strands, it produces mutations in the offspring RNA. This leaves the virus unable to translate the mutated RNA into proteins which eventually is lethal for the virus and ceases its spread as explained above. This effect is more prominent with higher concentrations of the drug. [18] This signifies the result of our analysis which demonstrates favorable outcomes in the virology profile only for 800mg and 400mg of molnupiravir, however, no significant result was reported with a 200mg dose of molnupiravir.

These findings are following the original studies by Arribas et al., and Caraco et al.*[6,14]*

The time for clearance of SARS-COV-2 was insignificant at all doses of molnupiravir. However, while considering this finding the methodological differences between trials should be kept in mind. One of the trials by Arribas et al., included in our meta-analysis had a patient population that consisted of hospitalized patients in whom the symptoms began 10 days before their inclusion in the trial while the rest of the trials included participants from the outpatient department (OPD) in whom the onset of symptoms was 5 days before their inclusion in the trial. [3,4,6,7,8,14]. The trial with the hospitalized patient population had non-significant outcomes while the trials that consisted of patients from the OPD tended to have better prognoses. This goes to show that molnupiravir might only be effective against SARS-CoV-2 if administered during the early days of the disease. All three of the previous meta-analyses were conducted on patients from the OPD and their results also show that molnupiravir had a significant effect in reducing mortality and hospitalization rate among those in the intervention group. [15,16,17]

In the preceding reviews, only a few adverse events were analyzed. These include any AEs, serious AEs, and discontinuation of the drug due to adverse events. Consistent with the results of previous meta-analyses, our analysis also shows that when compared to a placebo, molnupiravir does not significantly increase the risk of development of these outcomes. Furthermore, we also weigh up the adverse effects of molnupiravir on various organ systems such as cardiac, respiratory, renal, GI, and CNS. This is another feature that is unique to our manuscript. According to our analysis, molnupiravir carries no such significant adverse effects in comparison to placebo. This is true for all three dosages which goes to show that even increasing the dose of molnupiravir does not significantly increase the risk of development of any of the aforementioned adverse outcomes. One significant and perhaps one of the most important findings from our analysis is the significantly lower incidence of death in patients who were treated with 400mg molnupiravir as compared to those administered placebo. These results provide a much clearer picture concerning the dangers and safety profile of molnupiravir and indicate that molnupiravir is safe to use in clinical practice as a form of antiviral therapy.

Several factors enhance the reliability of our results. Firstly, we only included RCTs in our analysis, which generally tend to have lesser confounders when compared to observational studies. Add to that, all of the trials included in our analysis were judged as having a low to moderate risk of bias. Moreover, we performed an exhaustive literature search, consisting of multiple databases which reduce the risk of publication bias. We observed low to moderate heterogeneity in all of our outcomes.

Despite our best efforts, this study has some limitations. Firstly, our analysis lacks sufficient power. Therefore, our findings should be considered rather exploratory than definitive. Secondly, we had to account for

methodological heterogeneity among trials, as such, we had to use a random-effects model for our analysis. Furthermore, there was one significant difference between our trials. Some of the trials consisted of hospitalized patients while the rest consisted of patients from the outpatient department (OPD) who had mild to moderate Covid-19 infection. Due to lack of power and insufficient number of studies a sub-group analysis comparing the effects of molnupiravir in both populations could not be performed. All of the trials included in this study excluded pregnant and lactating patients which is why no pregnancy-related adverse events or teratogenic effects of the drug could be evaluated. Patients with SARS-CoV-2 vaccinations were also not available in any of the trials so a drug interaction between the vaccine and molnupiravir could not be studied.

Future Implications

Currently, two treatment options for SARS-CoV-2 are being extensively studied; molnupiravir and monoclonal antibodies (mAbs) (bamlanivimab–etesevimab, casirivimab–imdevimab, and sotrovimab) and both of these agents have shown promising results. [19,20] In trials, mAbs have been shown to reduce the risk of hospitalization, and death and have also demonstrated virological benefit by reducing the viral load. Similar results were seen with molnupiravir in the MOVE-OUT trial. However, molnupiravir being an oral drug would be more convenient for use as compared to mAbs. mAbs require intravenous infusion and thus can only be administered in the presence of trained medical personnel. mAbs are an expensive class of drugs and therefore their availability in countries with fewer resources might also be an issue. Furthermore, the efficacy of mAbs against the changing variants is also in doubt because these drugs work by binding to the spike proteins on SARS-CoV-2, and mutations in the spike proteins might affect their potency. Moreover, molnupiravir work by targeting the RdRp of the virus and is thus independent of mutations in the spike proteins.

Future trials should comprise of large sample sizes so a more robust idea about the dangers and potency of molnupiravir in Covid-19 positive patients could be achieved.

Conclusion: In our meta-analysis, we conclude that molnupiravir is most effective in treating SARS-COV-2 patients with respect to eliminating the virus from the host through their mechanism of action. Thereby, widely used and appropriate to treat SARS-COV-2. The results demonstrate the efficacy of molnupiravir in the hierarchy of dosages administered. The 800mg is more potent to create viral RNA error rate, likewise the 400mg dose. Furthermore, for mean change in SARS-COV-2 RNA viral load in the nasopharyngeal sample from baseline is also significant for 800mg and 400mg molnupiravir. However, none of the 200mg molnupiravir holds efficacy in reducing or altering the viral RNA to treat the patients of SARS-COV-2. Similarly, the promising result of 400mg molnupiravir reduces the incidence of death in SARS-COV-2 patients. Thereby the outcome depicts that molnupiravir could be a potential treatment for SARS-COV-2 patients.

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Conflict of interest: None

Authors Contribution:

Conceptualization : Mahnoor Sukaina; *Data curation* : Mahnoor Sukaina and Syeda Tayyab Rehan. *Formal analysis* : Mahnoor Sukaina. *Investigation* : Mahnoor Sukaina. *Methodology* : Mahnoor Sukaina. *Software* : Mahnoor Sukaina, Sidhart Ochani. *Project administration and Supervision* : Mahnoor Sukaina. . *Writing—original draft* : Mahnoor Sukaina, Syeda Tayyab Rehan, Syed Hasan Shuja, Sidhart Ochani Muhammad Shehryar, *Writing—review & editing* : Mahnoor Sukaina, Syeda Tayyaba Rehan.

Bibliography

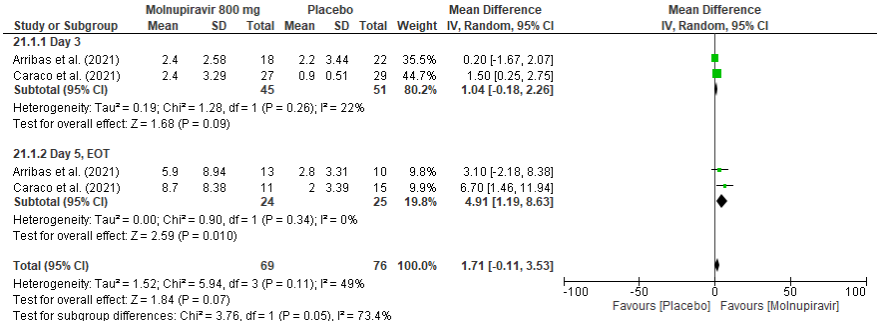
1. Coronavirus disease (COVID-19) – World Health Organization. Who.int. Accessed July 6, 2023. https://www.who.int
2. Sukaina M, Hasan MM, Essar MY. Emergence of Omicron BA.1 and BA.2 variants and concern over vaccine breakthr
3. Zou R, Peng L, Shu D, et al. Antiviral efficacy and safety of molnupiravir against Omicron variant infection: A rando
4. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospita

1. Coronavirus disease (COVID-19) – World Health Organization. Who.int. Accessed July 6, 2023. https://www.who.int
5. Siddiqui A, Adnan A, Abbas M, Taseen S, Ochani S, Essar MY. Revival of the heterologous prime-boost technique in
6. Caraco Y, Crofoot GE, Moncada PA, et al. Phase 2/3 trial of molnupiravir for treatment of covid-19 in nonhospitalize
7. Fischer WA 2nd, Eron JJ Jr, Holman W, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 sl
8. Khoo SH, Fitzgerald R, Fletcher T, et al. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-
9. Painter WP, Holman W, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel br
10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses
11. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane
12. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. Cochrane.org. Accessed July 6, 2023. https://meth
13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):
14. Arribas JR, Bhagani S, Lobo SM, et al. Randomized trial of molnupiravir or placebo in patients hospitalized with cov
15. Pitre T, Van Alstine R, Chick G, et al. Antiviral drug treatment for nonsevere COVID-19: a systematic review and n
16. Lai CC, Wang YH, Chen KH, Chen CH, Wang CY. The clinical efficacy and safety of anti-viral agents for non-hospita
17. Wen W, Chen C, Tang J, et al. Efficacy and safety of three new oral antiviral treatment (molnupiravir, fluvoxamine a
18. Tian L, Pang Z, Li M, et al. Molnupiravir and its antiviral activity against COVID-19. *Front Immunol*. 2022;13:85549
19. Gottlieb RL, Nirula A, Chen P, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on
20. RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Casirivimab and imdevimab in patients admitted to

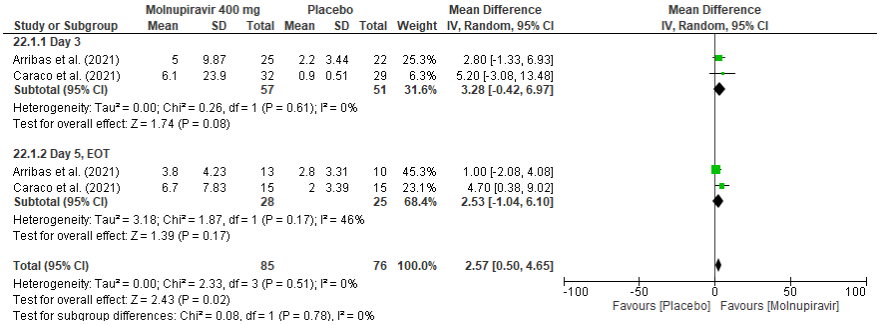
Forest Plots:

Figure 2: SARS-COV-2 RNA ERROR RATE

Molnupiravir 800 mg



(B)Molnupiravir 400 mg



(C) Molnipiravir 200 mg

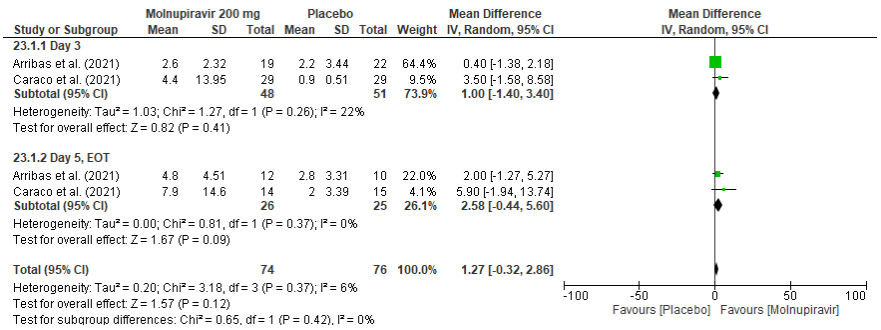
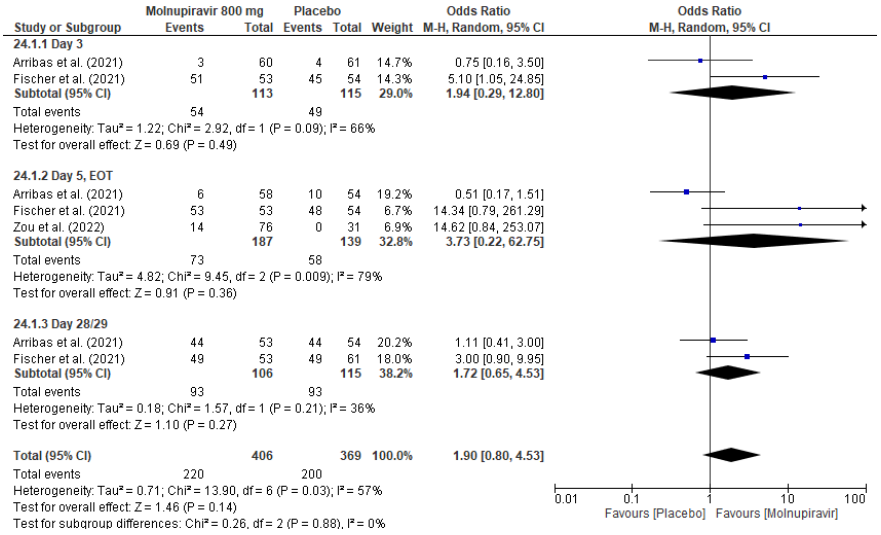
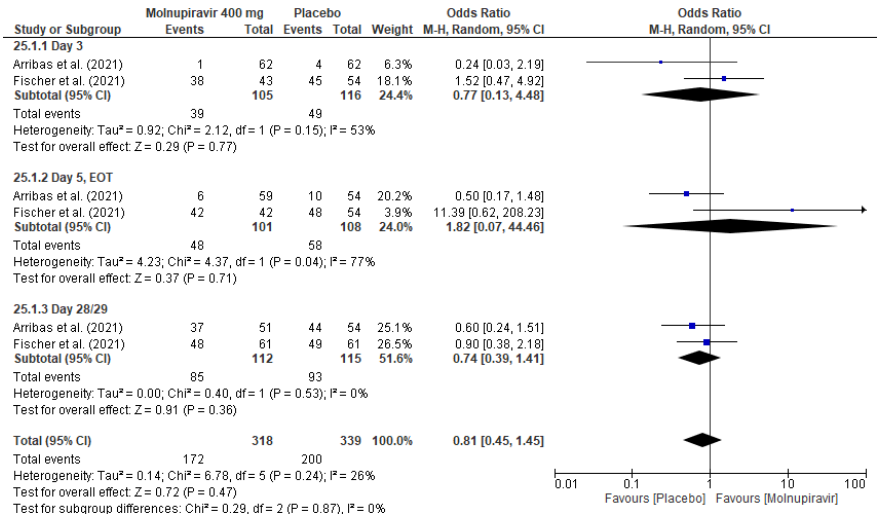
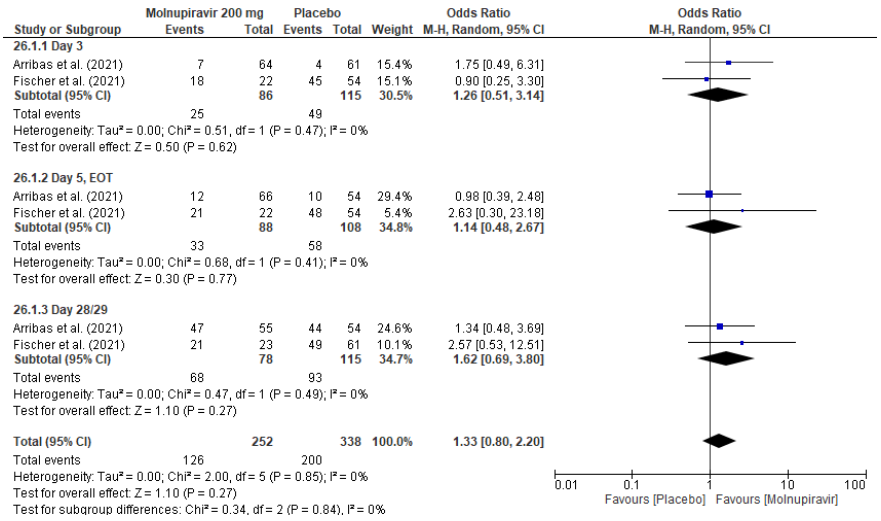


Figure 3: Time for clearance of SARS-COV-2 or undetectable SARS-COV-2 in the nasopharyngeal sample

(A) Molnupiravir 800 mg





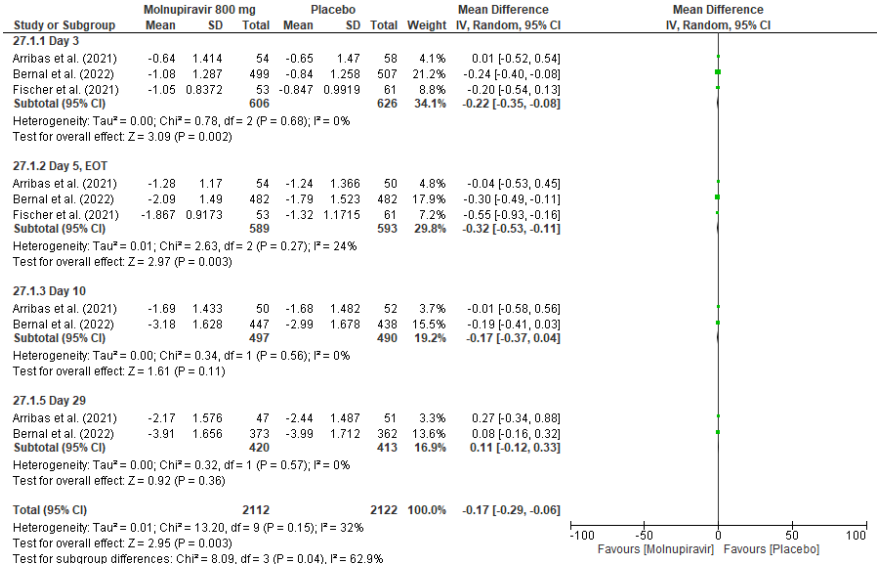


Molnupiravir 400 mg

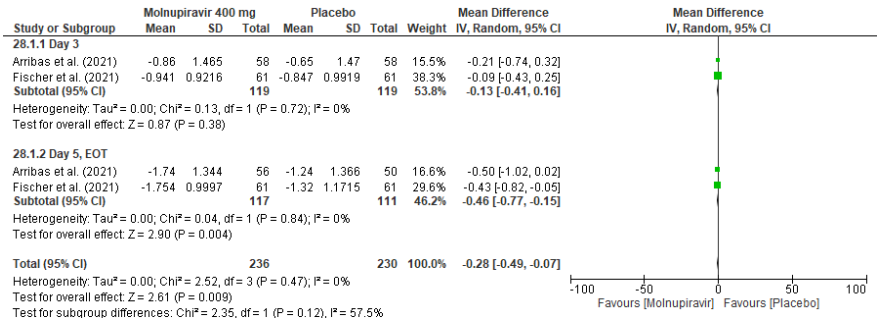
Molnupiravir 200 mg

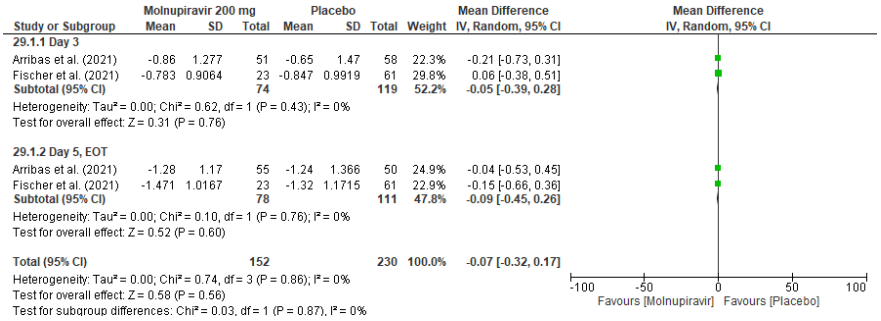
Figure 4: Mean change in SARS-COV-2 from baseline in nasopharyngeal sample

Molnupiravir 800 mg



Molnupiravir 400 mg





(C) Molnupiravir 200 mg

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Table 1. Baseline Characteristics.docx available at https://authorea.com/users/638156/articles/654056-virology-and-safety-profile-of-molnupiravir-at-three-different-doses-a-systematic-review-and-meta-analysis