International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 17, Issue 3, 2025

Review Article

# A COMPREHENSIVE REVIEW OF MOLNUPIRAVIR, NOVEL ANTIVIRAL DRUG FOR COVID-19

**AJAY KUMAR SHUKLA[1], SAURAV MISRA[2*]**

[1]Department of Pharmacology, AIIMS Bhopal, India. [2]Department of Pharmacology, Kalpana Chawla Government Medical College, Karnal, India

*Corresponding author: Saurav Misra; *Email: saurav181087@gmail.com

*Received: 23 Jan 2025, Revised and Accepted: 14 Mar 2025*

**ABSTRACT**

Effective oral antiviral drugs are still lacking despite improvements in COVID-19 management. Finding efficient and safe treatment against COVID-19 has become more important as a result of the discovery of novel SARS-CoV-2 mutations and the reporting of individuals with severe illness. A well-known viral RdRp inhibitor called molnupiravir has remarkably mutagenic effects on viral RNA. In the ongoing hunt for innovative antiviral drugs with acceptable efficacy and safety profiles against COVID-19, RdRp has been a priority target due to its significant role in the replication and transcription process of SARS-CoV-2 RNA. The possible evidences of efficacy and safety of molnupiravir in the treatment of COVID-19 are explored in the current review.

**Keywords:** Molnupiravir, COVID-19, Evidences of efficacy and safety


DOI: https://dx.doi.org/10.22159/ijcpr.2025v17i3.55037 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

## INTRODUCTION

The new Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the cause of Coronavirus Disease 2019 (COVID-19), one of the most deadly viral illnesses in recent history. On March 11, 2020, the World Health Organisation (WHO) proclaimed SARS-CoV-2 a pandemic [1]. The SARS-CoV-2 virus is undergoing evolution, and emerging strains persist as a significant global danger. The COVID-19 vaccinations have been demonstrated to be highly efficient in preventing the disease. Nevertheless, potent antiviral medications are presently under development for the treatment of COVID-19 [2]. Most COVID-19 patients typically recuperate from acute infection with limited medical intervention [3]. Nonetheless, clinical advancement to a critical state necessitating hospitalisation has significant ramifications for both human health (including morbidity and death) and healthcare systems. Consequently, reducing fatalities is the paramount concern of the current outbreak. The most effective preventive measures are COVID-19 vaccinations, which diminish the likelihood of hospitalisation and mortality [4-6]. Few alternative therapies have demonstrated efficacy in reducing this risk unless they are commenced quickly following the onset of symptoms [7]. The US Food and Drug Administration (US-FDA) has granted emergency use authorisation (EUA) for three monoclonal antibodies (MABs). This is intended for the treatment of mild to moderate COVID-19 in patients under 12 y of age (weighing less than 40 kg) with laboratory-confirmed SARS-CoV-2 infection who are at high risk for severe COVID-19 and/or hospitalisation. The disadvantages of these monoclonal antibodies (MABs) encompass the necessity for intravenous or subcutaneous delivery and the obligation for patients to be monitored for purported hypersensitivity (infusion-related events, including anaphylactic) reactions for a minimum of one-hour post-infusion. This limits their application in outpatient settings, as monoclonal antibodies are few beyond their origin and less efficacious against newly emerging diseases. A recent investigation evaluating the susceptibility of the Delta variant to the humoral immune response indicates that numerous monoclonal antibodies targeting the N-terminal and receptor binding domains of the spike protein exhibit diminished binding and neutralisation efficacy [8]. This indicates that certain monoclonal antibody treatments may be less effective against the novel SARS-CoV-2 variant [9]. Remdesivir is the only antiviral drug authorised by the US-FDA for the treatment of COVID-19 requiring hospitalisation in adults and children aged 12 y and older, weighing at least 40 kg. Remdesivir must be administered intravenously in a medical facility under stringent supervision. To address these concerns, two novel oral antiviral medicines, molnupiravir and nirmatrelvir in conjunction with ritonavir, have been developed for immediate administration to patients at home. On December 28, 2021, the Central Drugs Standard Control Organisation (CDSCO) of India awarded limited-use authorisation (RUA) for Molnupiravir. These drugs appear to be an essential addition to the COVID-19 therapy repertoire [10]. Molnupiravir was identified and initially developed in 2013 during the search for an oral antiviral agent to combat encephalitic New World alphavirus Venezuelan equine encephalitis virus (VEEV) infection. It received authorisation from the UK's Medicines and Health Products Regulatory Agency (MHRA) on November 4, 2021, for the treatment of COVID-19 patients to prevent adverse outcomes such as hospitalisation and mortality [6]. The NIH also recommended the medication for COVID-19 treatment. The highly contagious nature of the virus, its associated morbidity and mortality, and the global emergency situation of the disease have all been considered in the design of this study [6, 11]. This review presents evidence of the safety and efficacy of molnupiravir in COVID-19 patients.

### Mechanism of action

Molnupiravir is a prodrug of beta-D-iso-propylester of N-4-hydroxycytidine (NHC). Upon ingestion, host kinases metabolise molnupiravir in the plasma to produce the cytidine nucleoside NHC analogue. NHC is subject to intracellular triphosphorylation upon entering host cells, resulting in the formation of NHC-TP, which is pharmacologically active and acts as a competitive substrate for the viral RNA-dependent RNA polymerase (RdRp) [12, 13]. NHC-TP is subsequently integrated into the viral RNA strand as NHC-monophosphate (NHC-MP). Viral error catastrophe, or viral lethal mutagenesis, arises from the incorporation of NHC-MP into viral RNA. It inhibits viral replication by accumulating mutations throughout the viral genome [14]. Numerous RdRp-targeting antivirals have been granted FDA approval for the treatment of various viral infections [15]. The ExoN generated by coronaviruses removes incorrectly integrated nucleotides from the elongating RNA 3' end, thereby diminishing the efficacy of nucleoside analogues against SARS-CoV-2 [16]. RdRp synthesises nascent RNA strands by attaching ribonucleosides to the 3′-hydroxyl terminus, resulting in the formation of RNA in a 5′-3′ direction [17]. During genome replication, the pyrimidine nucleoside analogue NHC-MP is incorporated into the RNA strand in place of either cytosine (C) or uracil (U) in the emerging positive or negative-sense chain. Cell culture models have shown a dose-dependent increase in G-to-A and C-to-U transitions in viral RNA following NHC therapy [18-20]. Numerous

studies have validated the antiviral efficacy of molnupiravir through lethal mutagenesis or viral error catastrophe [21-37].

**Antiviral spectrum**

The active metabolite of molnupiravir exhibits significant antiviral efficacy against various RNA virus families while exerting no detrimental effects on DNA polymerases or DNA viruses. Flaviviruses (hepatitis C), togaviruses (Mayaro virus), alphaviruses (Chikungunya virus, Venezuelan equine encephalitis virus), filoviruses (Ebola virus), caliciviruses (norovirus), orthomyxoviruses (influenza A and B viruses), pneumoviruses (RSV), and coronaviruses (seasonal, Middle East Respiratory Syndrome virus, and SARS-CoV-1 and-2) are all vulnerable to this medication. The effective concentration 50% (EC50) ranged from 1 to 2 μM for various COVID-19 variants, including the Wa-1 strain and variants of concern such as alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), lambda (C.37), mu (B.1.621), and omicron (B.1.1.529/BA.1 and BA1.1) strains. Furthermore, strains possessing mutations that diminished their sensitivity to remdesivir exhibited no decline in the in vitro efficacy of molnupiravir. Nonetheless, neither the RSV nor influenza viruses have developed low-level resistance to NHC; only the VEEV and MERS viruses have done so. The observed low levels of resistance were associated with many transition mutations identified throughout the viral genome, indicating a strong resistance barrier. Resistance to Molnupiravir has not yet been identified in clinical investigations [37].

**Preclinical**

***In vitro***

NHC has exhibited significant antiviral efficacy against many coronaviruses, including SARS-CoV, SARS-CoV-2, and MERS-CoV, in trials utilising primary human cells and other cell lines. In the human lung epithelial cell line Calu-3 and Vero cells, the 50% inhibitory concentration (IC50) of molnupiravir against SARS-CoV-2 was 0.08 μM and 0.3 μM, respectively [38]. NHC exhibits an EC50 of 0.3 μM and 0.4 μM against Vero E6-GFP and Huh7 cells infected with the SARS-CoV-2 virus, respectively [39]. Do *et al.* discovered that EIDD-1931 may reduce viral RNA replication and diminish infectious virus titers in a dose-dependent manner using human tracheal airway epithelial cells (HtAEC) and human small airway epithelial cells (HsAEC) [40]. Zhao *et al.* established that molnupiravir exhibited a 0.22 μM EC50 and effectively suppressed SARS-CoV-2 RdRp utilising a Gluc reporter system dependent on SARS-CoV-2 RdRp [41]. Cox *et al.* investigated the efficacy of NHC against a clinical isolate of SARS-CoV-2 in cell culture, revealing EC50 and EC90 values of 3.4 μM and 5.4 μM, respectively [42]. The aforementioned results underscored the importance of NHC in clinical research by illustrating its efficacy and low cytotoxicity against SARS-CoV-2 across various cell lines.

***In vivo* investigations**

Ferrets and cynomolgus monkeys exhibit favourable pharmacokinetic properties for Molnupiravir (EIDD-2801), and the oral pharmacokinetic profile of ferrets following a single ascending dose may be employed to determine the optimal dosage for clinical trials. In ferrets, lung concentrations of Beta-d-N4-hydroxycytidine (EIDD-1931) reached 10.7–1.2 nmol/g following a single oral administration of EIDD-2801 at a dosage of 128 mg/kg. Following 7 d of bi-daily administration of EIDD-2801 at a dosage of 100 mg/kg, ferrets exhibited good tolerance with no apparent side effects. EIDD-2801 has efficient biodistribution and metabolism in vivo, as evidenced by Toots *et al.* The EC50 value of NHC for airway epithelial cells was approximately 0.06-0.08 μM, while the CC50 value was 137 μM. They created a well-differentiated human airway epithelial model cultivated at an air-liquid interface (ALI), that exhibits both the morphological and cellular attributes of authentic lung tissues [21, 43]. Rosenke *et al.* identified similar NHC/EIDD-1931 concentrations in the lungs of all treated animals; however, EIDD-2801 was not present since it rapidly hydrolysed to NHC [44]. Wahl *et al.* utilised human lung tissue transplanted in immunosuppressed rats (LoM model) to create a SARS-CoV-2 replication system. A comprehensive examination of LoM human lung tissue demonstrated that acute SARS-CoV-2 infection is extremely pathogenic, eliciting a substantial and prolonged chemokine response characterised by type I interferons and inflammatory cytokines. Therapeutic data indicate that molnupiravir/EIDD-2801 therapy significantly diminished the quantity of infectious particles in LoM human lung tissue by about 25,000-fold (p=0.0002). Initiating therapy 48 h post-exposure resulted in a significant reduction of viral titers by 96% (P=0.0019). The earlier molnupiravir treatment commenced after SARS-CoV-2 infection, the greater the reduction in viral replication observed. Molnupiravir diminished the viral titer by over 100,000-fold, as indicated by research findings on its preventive application [45]. Sheahan *et al.* employed a C57BL/6 mouse model with prophylactic and therapeutic dose escalation to demonstrate that the administration of EIDD-2801, either prophylactically or therapeutically, significantly mitigated or averted body weight loss, substantially reduced lung haemorrhage, and lowered viral titers in the lungs following SARS-CoV infection. The study revealed that the therapeutic benefit is affected by the duration of treatment initiation following the onset of an infection [46]. EIDD-2801 shown equivalent efficacy in inhibiting SARS-CoV-2 replication in a Syrian hamster model, with lung tissue analysis indicating a substantial reduction in viral RNA genome copy number and infectious virus levels. The mean viral antigen signal in vehicle groups was 4.71 times more than in drug prevention groups and 3.68 times higher, as per immunohistochemistry (IHC) analyses. The viral antigen concentration in the vehicle control group was significantly higher than that in the treatment group [44]. Abdelnabi *et al.* evaluated the effectiveness of molnupiravir against various SARS-CoV-2 strains, including the Wuhan strain, B.1.1.7, and B.1.351 variations, using the Syrian hamster infection model. Molnupiravir therapy markedly diminished viral RNA copies and infectious virus titers in the lung, irrespective of the SARS-CoV-2 variations [39].

Oral NHC medication significantly decreased viral levels in an alternative ferret study assessing the efficiency of treatments against the influenza virus. Mice administered NHC exhibited reduced levels of inflammation, histopathology, and fever in comparison to the control group. In the evaluation of influenza virus dissemination to small airways, the therapeutic application of NHC significantly diminished influenza virus titers in bronchioloalveolar lavage fluid and lung tissue samples [43]. Another study found that EIDD-2801 may significantly reduce the load of SARS-CoV-2 in the upper respiratory tract and effectively inhibit the virus's transmission in ferrets. Investigations utilising a ferret model infected with SARS-CoV-2 revealed that molnupiravir treatment exhibited no discernible adverse effects, and the subjects' white blood cell and platelet counts remained within normal parameters [42]. Moreover, many studies employing disease-relevant mouse, ferret, and human airway epithelial models have evidenced the drug's therapeutic and prophylactic activity against influenza A and B virus infections [43, 47, 48].

Ex-vivo research employing cryopreserved human lung tissues, characterised by diverse interleukin (IL-6, IL-8) and interferon (IFN)-B1 production analogous to SARS-CoV-2 infection, was conducted to ascertain the efficacy of NHC in inhibiting viral proliferation [49]. Molnupiravir's effectiveness in mitigating the transmission of SARS-CoV-2 was evidenced by the absence of viral infection in the nasal tissues and secretions of a ferret model exhibiting minor clinical symptoms akin to those of the young-adult human demographic. Numerous further trials have demonstrated the advantages of molnupiravir compared to other anti-SARS-CoV-2 medications [49, 51-53].

**Clinical trials**

**Phase 1**

In the preliminary double-blind, randomized-controlled Phase 1 trial, which included 130 healthy participants, moln1upiravir was well tolerated. Post-injection, pharmacokinetics exhibited dosage proportionality. Following oral administration, the prodrug molnupiravir was rapidly converted into its active form EIDD-1931, with a median time to maximum measured concentration of 1-1.7 h. No accumulation was observed with repeated dosage, which has a geometric half-life of roughly 1 h and an apparent delayed clearance phase after high single or multiple doses. It was demonstrated to be both safe and well-tolerated to provide a single dose of up to 1600

mg and a range of 50-800 mg twice daily for 5.5 d. The limited detection of EIDD-1931 in urine may be attributed to its metabolism into cytidine and uridine rather than other nucleoside analogues and natural nucleosides, which are commonly excreted by the kidneys. In terms of tolerability, a greater proportion of patients in the placebo group reported adverse effects following a single dose of molnupiravir (43.8% compared to 35.4%) and after receiving multiple ascending doses (50.0% compared to 42.9%). The predominant adverse event noted in the single ascending dose study was headache (18.8% compared to 12.5%), whereas the most often reported adverse event in the multiple ascending dosage study was diarrhoea (7.1% in both the molnupiravir and placebo cohorts) [54].

A separate open-label, phase Ib/IIa randomised controlled trial (AGILE) with a limited sample size (n = 18) was executed at the Royal Liverpool and Broadgreen Clinical Research Centre employing a Bayesian methodology. Adult patients with RT-PCR confirmed SARS-CoV-2 infection were randomly assigned to receive standard of care (SOC; n = 6) or 300, 600, or 800 mg of molnupiravir administered orally twice daily for five days (n = 4 in each group). This was accomplished within five days after symptom start. All (4/4, 100%) patients administered 300 and 600 mg, 1/4 (25%) of those getting 800 mg, and 5/6 (83%) of patients undergoing standard of care (SOC) experienced mild adverse effects. Consequently, molnupiravir was determined to be well tolerated and safe, with a plasma concentration within the target range. The probability that the maximal dosage of 800 mg administered twice day would result in 30% greater harm than the controls was 0.9% [55].

A phase IIa, double-blind, randomized-controlled, multicentric trial (n=202) was performed to assess the safety and tolerability of molnupiravir in individuals with mild to moderate COVID-19. Participants were randomly allocated to receive either 200 mg of molnupiravir or a placebo, or 400 mg or 800 mg of molnupiravir or a placebo, administered bi-daily for five days. Individuals administered 800 mg of molnupiravir exhibited significantly reduced viral isolation at Day 3 (p = 0.02) in contrast to those receiving a placebo (16.7%). On Day 5, 11.1% of persons administered a placebo exhibited viral isolates, but no patients receiving 400 or 800 mg of molnupiravir presented any viral isolates (p = 0.03). A higher overall percentage of viral RNA clearance and a faster time to clearance were seen in individuals administered 800 mg of molnupiravir compared to those who received a placebo (p = 0.01). Overall, molnupiravir was well tolerated, with the incidence of adverse events being comparable across all groups [56]. The phase 3 double-blind, randomised study (MOVe-OUT) was recently terminated by the independent data safety monitoring board after evaluating the efficacy and safety of molnupiravir in 1850 non-hospitalized adult participants (18 y or older) with COVID-19, due to an excessive benefit observed in the active treatment group relative to the placebo [57].

The interim analysis of this phase 3 study (n = 775) revealed a 50% significant decrease in the probability of hospital admission or mortality by day 29 (p = 0.0012). In the study, patients administered a placebo (53/377) exhibited a death rate of 14.1%, whereas those treated with molnupiravir (28/385) demonstrated a hospitalisation rate of 7.3%. On day 29, there were no fatalities recorded in the molnupiravir group, whereas the placebo group saw 8 deaths. The effectiveness of molnupiravir remained unchanged by the SARS-CoV-2 variants (gamma, delta, or mu), the timing of symptom onset, or the preexisting risk factors. The incidence of overall adverse events was 35% in the molnupiravir arm and 40% in the placebo arm, while drug-related adverse events were 12% in the molnupiravir arm and 11% in the placebo arm, indicating comparability between the two groups [58, 59]. A phase 3 double-blind, randomised study (MOVe-IN, NCT04575584) aimed at evaluating the efficacy and safety of molnupiravir in 304 hospitalised adults (18 y or older) with COVID-19 (MK-4482-001) was terminated following an interim data analysis indicating an improbable clinical benefit for hospitalised patients [60].

Optimus Pharma publicly released an additional intermediate report from the phase 3 study of molnupiravir in mild COVID-19 patients from India (CTRI/2021/06/033992) on July 21, 2021. The initial interim results from 353 patients [61] indicated that on day 5, the proportion of RT-PCR negative cases in the molnupiravir group was greater than in the standard of care group alone (78.3% vs. 48.4%; p = not provided). A second interim analysis included 403 patients revealed no significant difference at day 14 (99.5% vs. 98.5%; p = 0.62). However, Optimus Pharma reported a substantial increase in RT-PCR negativity with molnupiravir compared to standard of care alone at days 5 and 10 (77.4% vs. 51.5%, p<0.0001 and 99.5% vs. 69.5%, respectively; p<0.0001). On days 5 and 10, both molnupiravir and standard of care (SOC) demonstrated more rapid clinical improvement, with at least a one-point enhancement from baseline on the WHO ordinal scale (p = 0.0001 and 97.8% versus 82.3%, respectively; p = 0.0001, respectively). In the SOC group, three patients encountered a serious adverse event, whereas only one patient in the molnupiravir arm did. In summary, molnupiravir expedited clinical and viral recovery (RT-PCR negative) compared to standard of care alone in moderate COVID-19, with no apparent drug-related side effects, as per interim findings from an ongoing open-label, randomised clinical trial in India [62]. In a separate phase 3 double-blind, randomised, placebo-controlled research, the effectiveness and safety of molnupiravir treatment were evaluated. A total of 1,433 trial participants were administered 800 mg of molnupiravir (n = 716) or a placebo (n = 717) alternatively twice day for a duration of 5 d. The interim analysis results demonstrated that molnupiravir exhibited superiority; the incidence of hospitalisation for any cause or mortality by day 29 was reduced with molnupiravir (28 of 385 participants; 7.3%) compared to placebo (53 of 377 participants; 14.1%) (difference,-6.8 percentage points; 95% confidence interval [CI],-11.3 to-2.4; P = 0.001) [63]. A retrospective cohort analysis was conducted involving all patients treated with molnupiravir at the University Hospital of Sassari from January 10, 2022, to March 31, 2022. A total of 192 individuals were enrolled, with an average age of 70.4 y; 75% of the participants, equating to 144, were above the age of 60. Molnupiravir demonstrated exceptional safety, with only one interruption and 13 (6.8%) documented side effects. This study established the efficacy and safety of monlupiravir in a real-world cohort characterised by a significant proportion of elderly persons and a considerable burden of comorbidities [64].

In a separate randomised, controlled trial included patients with mild to moderate COVID-19. On the fifth day of medication, participants receiving molnupiravir had a viral RNA clearance of 18.42%, in contrast to 0% in the control group (p = 0.0092). On day 7, the proportion of patients in the molnupiravir-treated group with eradicated viral RNA was 40.79%, compared to 6.45% in the control group (p = 0.0004). Furthermore, there have been no documented instances of significant adverse events [65].

**Spe**

**Gestation and breastfeeding**

Currently, there is no data about the administration of molnupiravir in pregnant or lactating women. Animal studies indicate that molnupiravir may increase the risk of foetal damage when given during pregnancy. A pregnant rat model was administered eight times the standard NHC treatment exposure (800 mg twice day), resulting in developmental toxicity, mortality, teratogenicity, and additional developmental complications. Additionally, in a pregnant rabbit model administered 18 times the standard dosage of NHC therapy, a decrease in foetal growth was seen. Although NHC was detected in the plasma of nursing rat pups, no effects on their growth, development, or behaviour were observed. Molnupiravir is contraindicated during pregnancy due to the potential risk of harm to the developing foetus. Women desiring to conceive should utilise effective contraception during therapy and for four days following its conclusion. In sexually active males with reproductive capability and partners capable of childbearing, effective contraceptive measures are recommended for a minimum of three months after the final administration of medication [66].

**Paediatric medicine**

Individuals under 18 y of age should refrain from using molnupiravir. Rats administered 500 mg/kg/day exhibited reduced bone resorption of growth cartilage in a three-month study (five times the human NHC

doses in the RHD). [66] In a brief one-month trial including mice and rats at elevated dosages (2,000 mg/kg/day [19 times human NHC exposure] and 500 mg/kg/day [4 to 8 times human NHC exposure], respectively), this effect was not observed in dogs after 14 d at dosages equal to human exposures (50 mg/kg/day). The lack of growth cartilage in mature bones renders these findings inapplicable to adults while potentially detrimental to younger individuals [66].

**Renal impairment**

The dosage of molnupiravir remains unchanged in persons with renal insufficiency. The kidneys do not substantially facilitate the elimination of the drug, although the pharmacokinetics have not been examined in individuals with severe renal impairment, including those undergoing dialysis. Population pharmacokinetic investigation did not reveal a significant effect of mild to moderate dysfunction on the pharmacokinetics of molnupiravir [66].

**Hepatic dysfunction**

The dosage of Molnupiravir remains unchanged for individuals with hepatic impairment [66].

**Adverse effect**

The sole data regarding the side-effect profile of molnupiravir is derived from clinical research. When the EUA was granted, merely 900 patients had been administered therapeutic doses, predominantly sourced from the phase 3 MOVe-OUT study. [66] In the MOVe-OUT study, molnupiravir had a predominantly favourable adverse event profile. Compared to 33% of patients administered a placebo, 30% of people treated with molnupiravir encountered at least one adverse event. Only 8.0% and 8.4% of all adverse events for molnupiravir and placebo, respectively, were deemed attributable to the study regimen. Severe adverse events were documented at 6.9% in the molnupiravir group compared to 9.6% in the placebo group, predominantly associated with COVID-19. No significant adverse events associated with the treatment regimen occurred among the patients, and none prompted them to cease their medication. The predominant side effects observed in the study (2.3% of patients in both cohorts) comprised diarrhoea (2.3% against 3.0%), COVID-19 pneumonia (6.3% compared to 9.6% in the molnupiravir cohort over the placebo), and bacterial pneumonia (2.0 versus 1.6%). The most common side effects attributed to the trial regimen were diarrhoea (1.7% versus 2.1%), nausea (1.4% versus 0.7%), and dizziness (1.0% against 0.7% of individuals). Participants in the MOVe-IN study who got molnupiravir (55.5%) or a placebo (61.3%) frequently encountered adverse events, and the researchers could not definitively ascertain whether adverse events were attributable to molnupiravir medication [63, 67].

## CONCLUSION

The existing data indicates that molnupiravir treatment may offer renewed optimism for COVID-19 recovery and has the potential to be a groundbreaking and very promising therapeutic option for COVID-19. Future trials of molnupiravir should consider its potential efficacy in COVID-19 patients, with monitoring for long-term adverse events, effects on bone and cartilage production, potential genotoxic effects, and its influence in both vaccinated and unvaccinated populations.

## ACKNOWLEDGEMENT

None

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All authors have contributed equally

## CONFLICT OF INTERESTS

Declared none

## REFERENCES

1. Shukla AK, Misra S. An overview of post COVID sequelae. J Basic Clin Physiol Pharmacol. 2022 Apr 15;33(6):715-26. doi: 10.1515/jbcpp-2022-0057, PMID 35428040.
2. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. Diabetes Metab Syndr. 2021 Dec;15(6):102329. doi: 10.1016/j.dsx.2021.102329, PMID 34742052.
3. Jayk Bernal A, Gomes DA, Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med. 2022 Feb 10;386(6):509-20. doi: 10.1056/NEJMoa2116044, PMID 34914868.
4. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network United States. MMWR Morb Mortal Wkly Rep. 2020;69(30):993-8. doi: 10.15585/mmwr.mm6930e1, PMID 32730238.
5. Rosenberg ES, Holtgrave DR, Dorabawila V, Conroy M, Greene D, Lutterloh E. New COVID-19 cases and hospitalizations among adults by vaccination status new York. MMWR Morb Mortal Wkly Rep. 2021 Aug 27;70(34):1150-5. doi: 10.15585/mmwr.mm7034e1, PMID 34437517.
6. Bajema KL, Dahl RM, Prill MM, Meites E, Rodriguez Barradas MC, Marconi VC. Effectiveness of COVID-19 mRNA vaccines against COVID-19-associated hospitalization five veterans affairs medical centers united states. MMWR Morb Mortal Wkly Rep. 2021;70(37):1294-9. doi: 10.15585/mmwr.mm7037e3, PMID 34529636.
7. Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. Viruses. 2021;13(4):628. doi: 10.3390/v13040628, PMID 33916927.
8. Recovery Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (Recovery): a randomised controlled open-label platform trial. Lancet. 2022 Feb 12;399(10325):665-76. doi: 10.1016/S0140-6736(22)00163-5, PMID 35151397.
9. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA. 2021 Feb 16;325(7):632-44. doi: 10.1001/jama.2021.0202, PMID 33475701.
10. Gupta A, Gonzalez Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med. 2021 Nov 18;385(21):1941-50. doi: 10.1056/NEJMoa2107934, PMID 34706189.
11. Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel Benhassine F, Rajah MM. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. Nature. 2021 Aug 12;596(7871):276-80. doi: 10.1038/s41586-021-03777-9, PMID 34237773.
12. European Centre for Disease Prevention and Control European Centre for Disease Prevention and Control (ECDC). Stockholm (Sweden): Risk assessment: SARSCoV-2-increased circulation of variants of concern and vaccine roll out in the EU/EEA, 14th update; 2021 Feb 15.
13. US Food and Drug Administration. In: Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab and etesevimab. Available from: https://www.fda.gov/media/145802/download. [Last accessed on 27 Jul 2023].
14. US Food and Drug Administration. Fact sheet health care providers emerg use authorization (EUA) regen-cov (Casirivimab with imdevimab). Available from https://www.fda.gov/media/145611/download. [Last accessed on 27 Jul 2023].
15. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature. 2022 Feb;602(7898):657-63. doi: 10.1038/s41586-021-04385-3, PMID 35016194.
16. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. Diabetes Metab Syndr. 2021;6(6):102329. doi: 10.1016/j.dsx.2021.102329, PMID 34742052.
17. Singh AK, Singh A, Singh R, Misra A. An updated practical guideline on use of molnupiravir and comparison with agents having emergency use authorization for treatment of COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2022;16(2):102396. doi: 10.1016/j.dsx.2022.102396.

18. Sharma P, Behl T, Sharma N, Singh S, Grewal AS, Albarrati A. COVID-19 and diabetes: association intensify risk factors for morbidity and mortality. Biomed Pharmacother. 2022 Jul;151:113089. doi: 10.1016/j.biopha.2022.113089, PMID 35569351.
19. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML. An orally bioavailable broad spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med. 2020 Apr 29;12(541):eabb5883. doi: 10.1126/scitranslmed.abb5883, PMID 32253226.
20. Painter GR, Natchus MG, Cohen O, Holman W, Painter WP. Developing a direct acting orally available antiviral agent in a pandemic: the evolution of molnupiravir as a potential treatment for COVID-19. Curr Opin Virol. 2021;50:17-22. doi: 10.1016/j.coviro.2021.06.003, PMID 34271264.
21. Tian L, Pang Z, LI M, Lou F, An X, Zhu S. Molnupiravir and its antiviral activity against COVID-19. Front Immunol. 2022;13:855496. doi: 10.3389/fimmu.2022.855496, PMID 35444647.
22. GOV UK. First oral antiviral for COVID-19 lagevrio (molnupiravir) approved by mhra. Available from: https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19lagevrio-molnupiravir-approved-by-mhra#:~:text=The%20antiviral%20Lagevrio%20(molnupiravir)%20is,Agency%20(MHRA)%20announced%20today. [Last accessed on 26 Jul 2023].
23. Merck news release. Merck and ridgebacks molnupiravir receives U. S. FDA emergency use authorization for the treatment of high risk adults with mild to moderate COVID-19. Available from: https://www.merck.com/news/merck-and-ridgebacks-molnupiravir-receives-u-s-fda-emergency-use-authorization-for-the-treatment-of-high-risk-adults-with-mild-to-moderate-covid-19. [Last accessed on 03 Mar 2023].
24. Antiviral Therapy. COVID-19 treatment guidelines. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy. [Last accessed on 03 Mar 2023].
25. Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon KH. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. Nature. 2021;591(7850):451-7. doi: 10.1038/s41586-021-03312-w, PMID 33561864.
26. Merck. Fact sheet for healthcare providers: emergency use authorization for molnupiravir]. Available from: https://www.com.merck/eua/molnupiravir-hcp-fact-sheet.pdf. [Last accessed on 03 Mar 2023]
27. Smith EC, Blanc H, Surdel MC, Vignuzzi M, Denison MR. Coronaviruses lacking exoribonuclease activity are susceptible to lethal mutagenesis: evidence for proofreading and potential therapeutics. Plos Pathog. 2013 Aug;9(8):e1003565. doi: 10.1371/journal.ppat.1003565, PMID 23966862.
28. Agostini ML, Pruijssers AJ, Chappell JD, Gribble J, LU X, Andres EL. Small-molecule antiviral β-d-n4-hydroxycytidine inhibits a proofreading-intact coronavirus with a high genetic barrier to resistance. J Virol. 2019;93(24):e01348-19. doi: 10.1128/JVI.01348-19, PMID 31578288.
29. Sledziewska Gojska E, Janion C. Effect of proofreading and dam instructed mismatch repair systems on N4-hydroxycytidine induced mutagenesis. Mol Gen Genet. 1982;186(3):411-8. doi: 10.1007/BF00729462, PMID 6750321.
30. Tejero H, Montero F, Nuno JC. Theories of lethal mutagenesis: from error catastrophe to lethal defection. Curr Top Microbiol Immunol. 2016;392:161-79. doi: 10.1007/82_2015_463, PMID 26210988.
31. Hashemian SM, Pourhanifeh MH, Hamblin MR, Shahrzad MK, Mirzaei H. RdRp inhibitors and COVID-19: is molnupiravir a good option? Biomed Pharmacother. 2022 Feb;146:112517. doi: 10.1016/j.biopha.2021.112517, PMID 34902743.
32. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML. An orally bioavailable broad spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med. 2020;12(541):eabb5883. doi: 10.1126/scitranslmed.abb5883, PMID 32253226.
33. Urakova N, Kuznetsova V, Crossman DK, Sokratian A, Guthrie DB, Kolykhalov AA. β-d-N4-Hydroxycytidine is a potent anti-alphavirus compound that induces a high level of mutations in the viral genome. J Virol. 2018;92(3):e01965-17. doi: 10.1128/JVI.01965-17, PMID 29167335.
34. Rosenke K, Hansen F, Schwarz B, Feldmann F, Haddock E, Rosenke R. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the syrian hamster model. Nat Commun. 2021;12(1):2295. doi: 10.1038/s41467-021-22580-8, PMID 33863887.
35. Gordon CJ, Tchesnokov EP, Schinazi RF, Gotte M. Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. J Biol Chem. 2021;297(1):100770. doi: 10.1016/j.jbc.2021.100770, PMID 33989635.
36. Kabinger F, Stiller C, Schmitzova J, Dienemann C, Kokic G, Hillen HS. Mechanism of molnupiravir induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol. 2021;28(9):740-6. doi: 10.1038/s41594-021-00651-0, PMID 34381216.
37. Atmar RL, Finch N. New perspectives on antimicrobial agents: molnupiravir and nirmatrelvir/ritonavir for treatment of COVID-19. Antimicrob Agents Chemother. 2022;66(8):e0240421. doi: 10.1128/aac.02404-21, PMID 35862759.
38. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML. An orally bioavailable broad spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med. 2020;12(541):eabb5883. doi: 10.1126/scitranslmed.abb5883, PMID 32253226.
39. Abdelnabi R, Foo CS, Kaptein SJ, Zhang X, DO TN, Langendries L. The combined treatment of molnupiravir and favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. E Biomedicine. 2021;72:103595. doi: 10.1016/j.ebiom.2021.103595, PMID 34571361.
40. DO TN, Donckers K, Vangeel L, Chatterjee AK, Gallay PA, Bobardt MD. A robust SARS-CoV-2 replication model in primary human epithelial cells at the air liquid interface to assess antiviral agents. Antiviral Res. 2021 Aug;192:105122. doi: 10.1016/j.antiviral.2021.105122, PMID 34186107.
41. Zhao J, Guo S, YI D, LI Q, MA L, Zhang Y. A cell based assay to discover inhibitors of SARS-CoV-2 RNA dependent RNA polymerase. Antiviral Res. 2021;190:105078. doi: 10.1016/j.antiviral.2021.105078, PMID 33894278.
42. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat Microbiol. 2021;6(1):11-8. doi: 10.1038/s41564-020-00835-2, PMID 33273742.
43. Toots M, Yoon JJ, Cox RM, Hart M, Sticher ZM, Makhsous N. Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. Sci Transl Med. 2019;11(515):eaax5866. doi: 10.1126/scitranslmed.aax5866, PMID 31645453.
44. Rosenke K, Hansen F, Schwarz B, Feldmann F, Haddock E, Rosenke R. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the syrian hamster model. Res Sq. 2020 Oct 8. doi: 10.21203/rs.3.rs-86289/v1, PMID 33052329.
45. Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon KH 3rd. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. Nature. 2021;591(7850):451-7. doi: 10.1038/s41586-021-03312-w, PMID 33561864.
46. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML. An orally bioavailable broad spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Sci Transl Med. 2020;12(541):eabb5883. doi: 10.1126/scitranslmed.abb5883, PMID 32253226.
47. Kumar D, Trivedi N. Disease drug and drug-drug interaction in COVID-19: risk and assessment. Biomed Pharmacother. 2021 Jul;139:111642. doi: 10.1016/j.biopha.2021.111642, PMID 33940506.
48. Ribeiro IG, Coelho Dos Reis JG, Fradico JR, Costa Rocha IA, Silva LD, Fonseca LA. Remodeling of immunological biomarkers in patients with chronic hepatitis C treated with direct acting antiviral therapy. Antiviral Res. 2021;190:105073. doi: 10.1016/j.antiviral.2021.105073, PMID 33887350.

49. Parsons TL, Kryszak LA, Marzinke MA. Development and validation of assays for the quantification of β-D-N4-hydroxycytidine in human plasma and β-D-N4-hydroxycytidine triphosphate in peripheral blood mononuclear cell lysates. J Chromatogr B Analyt Technol Biomed Life Sci. 2021;1182:122921. doi: 10.1016/j.jchromb.2021.122921, PMID 34555541.
50. Schaller MA, Sharma Y, Dupee Z, Nguyen D, Uruena J, Smolchek R. Ex vivo SARS-CoV-2 infection of human lung reveals heterogeneous host defense and therapeutic responses. JCI Insight. 2021;6(18):e148003. doi: 10.1172/jci.insight.148003, PMID 34357881.
51. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. Nat Microbiol. 2021;6(1):11-8. doi: 10.1038/s41564-020-00835-2, PMID 33273742.
52. Ebenezer O, Jordaan MA, Ogunsakin RE, Shapi M. Potential SARS-COV preclinical (in vivo) compounds targeting COVID-19 main protease: a meta-analysis and molecular docking studies. Hippokratia. 2020;24(3):99-106. PMID 34239286.
53. Han B, Song Y, LI C, Yang W, MA Q, Jiang Z. Safety tolerability and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: a double blind randomised controlled phase 1/2 clinical trial. Lancet Infect Dis. 2021 Dec;21(12):1645-53. doi: 10.1016/S1473-3099(21)00319-4, PMID 34197764.
54. Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Eraut NC. Human safety tolerability and pharmacokinetics of molnupiravir a novel broad spectrum oral antiviral agent with activity against SARS-CoV-2. Antimicrob Agents Chemother. 2021 May 1;65(5):e02428-20. doi: 10.1128/AAC.02428-20, PMID 33649113.
55. Khoo SH, Fitzgerald R, Fletcher T, Ewings S, Jaki T, Lyon R. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose escalating randomized controlled study. J Antimicrob Chemother. 2021 Nov 12;76(12):3286-95. doi: 10.1093/jac/dkab318, PMID 34450619.
56. Fischer W, Eron JJ, Holman W, Cohen MS, Fang L, Szewczyk LJ. Molnupiravir an oral antiviral treatment for COVID-19. medRxiv; 2021 Jun 17;2021:21258639. doi: 10.1101/2021.06.17.21258639.
57. Clinical trials. The safety of molnupiravir (EIDD-2801) and its effect on viral shedding of SARS-CoV-2. Available from: https://clinicaltrials.gov/ct2/show/NCT04405739. [Last accessed on 3 Mar 2023].
58. Merck. Com Merck and ridgeback's investigational oral antiviral molnupiravir reduced the risk of hospitalization or death by approximately 50 percent compared to placebo for patients with mild or moderate COVID-19 in positive interim analysis of phase 3 study. Available from: https://www.merck.com/news/merckand-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-riskof-hospitalization-or-death-by-approximately-50-percent-compared-toplacebo-for-patients-with-mild-or-moderat. [Last accessed on 3 Mar 2023].
59. Merck. Merck and ridgeback biotherapeutics provide update on progress of clinical development program for molnupiravir an investigational oral therapeutic for the treatment of mild to moderate COVID-19. Available from: https://www.merck.com/news/merck-and-ridgeback-biotherapeutics-provide-update-on-progress-of-clinical-development-program-for-molnupiravir-aninvestigational-oral-therapeutic-for-the-treatment-of-mild-to-moderate-covid-19/#:~:text=Merck%20and%20Ridgeback%20Biotherapeutics%20plan.
60. Clinical Trail. A phase III, randomized multi-centre double blind placebo controlled study to evaluate efficacy safety and immunogenicity of novel corona virus-2019-nCov vaccine candidate of M/s cadila healthcare limited. Available from: https://ctri.nic.in/clinicaltrials/showallp.php?mid1=51254andEncHid=anduserName=ZyCoV-D. [Last accessed on 26 Jul 2023].
61. The Print. Optimus announces interim clinical results from phase III clinical trials of molnupiravir conducted in India. Available from: www.//https.print.in/ani-press-releases/optimus-announces-interim-clinical-results-from-phase-iii-clinical-trials-of-molnupiravir-conducted-in-india/699993. [Last accessed on 3 Mar 2023].
62. Jayk Bernal A, Gomes DA Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 2022 Feb 10;386(6):509-20. doi: 10.1056/NEJMoa2116044, PMID 34914868.
63. DE Vito A, Colpani A, Bitti A, Zauli B, Meloni MC, Fois M. Safety and efficacy of molnupiravir in SARS-CoV-2-infected patients: a real life experience. J Med Virol. 2022 Nov;94(11):5582-8. doi: 10.1002/jmv.28011, PMID 35855627.
64. Zou R, Peng L, Shu D, Zhao L, Lan J, Tan G. Antiviral efficacy and safety of molnupiravir against omicron variant infection: a randomized controlled clinical trial. Front Pharmacol. 2022 Jun 15;13:939573. doi: 10.3389/fphar.2022.939573, PMID 35784723.
65. Merck. Fact sheet for healthcare providers: emergency use authorization for molnupiravir. Com. Available from: https://www.merck/eua/molnupiravir-hcp-fact-sheet.pdf. [Last accessed on 03 Mar 2023].
66. Merck. Merck briefing information for the Nov 30 2021 meeting of the antimicrobial drugs advisory committee. Available https://www.fda.gov/media/154421/download. [Last accessed on 03 Mar 2023].
67. Arribas JR, Bhagani S, Lobo SM, Khaertynova I, Mateu L, Fishchuk R. Randomized trial of molnupiravir or placebo in patients hospitalized with covid-19. NEJM Evid. 2022;1(2):EVIDoa2100044. doi: 10.1056/EVIDoa2100044, PMID 38319178.