



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Review Article

# An updated practical guideline on use of molnupiravir and comparison with agents having emergency use authorization for treatment of COVID-19<sup>☆</sup>

Awadhesh Kumar Singh <sup>a,\*</sup>, Akriti Singh <sup>b</sup>, Ritu Singh <sup>a</sup>, Anoop Misra <sup>c,d,e</sup><sup>a</sup> G. D Hospital & Diabetes Institute, Kolkata, West Bengal, India<sup>b</sup> Jawaharlal Nehru Medical College & Hospital, Kalyani, West Bengal, India<sup>c</sup> Fortis C-Doc Hospital for Diabetes & Allied Sciences, New Delhi, India<sup>d</sup> National Diabetes, Obesity and Cholesterol Foundation, New Delhi, India<sup>e</sup> Diabetes Foundation (India), New Delhi, India

## ARTICLE INFO

## Article history:

Received 10 January 2022

Received in revised form

11 January 2022

Accepted 11 January 2022

## Keywords:

Molnupiravir

Remdesivir

Casirivimab–imdevimab

Bamlanivimab–etesevimab

Sotrovimab

Nirmatrelvir–ritonavir

COVID-19

SARS-CoV-2

## ABSTRACT

**Background and aims:** Molnupiravir is a newer oral antiviral drug that has recently received emergency use authorization (EUA) in USA, UK and India. We aim to conduct an update on our previous systematic review to provide practical clinical guideline for using molnupiravir in patients with COVID-19.

**Methods:** We systematically searched the electronic database of PubMed, MedRxiv and Google Scholar until January 5, 2022, using key MeSH keywords.

**Results:** Final result of phase 3 study in 1433 non-hospitalized COVID-19 patients showed a significant reduction in composite risk of hospital admission or death (absolute risk difference,  $-3.0\%$  [95% confidence interval {CI},  $-5.9$  to  $-0.1\%$ ; 1-sided  $P = 0.02$ ) although with a non-significant 31% relative risk reduction (RRR). RRR for death alone was 89% (95% CI, 14 to 99;  $P$ -value not reported). Number needed to treat to prevent 1 death or 1 hospitalization or death composite appears to be closely competitive to other agents having EUA in people with COVID-19. However, cost-wise molnupiravir is comparatively cheaper compared to all other agents.

**Conclusion:** Molnupiravir could be a useful agent in non-pregnant unvaccinated adults with COVID-19 who are at increased risk of severity including hospitalization. However, it is effective only when used within 5-days of onset of symptoms. A 5-days course seems to be safe without any obvious short-term side effects.

© 2022 Diabetes India. Published by Elsevier Ltd. All rights reserved.

## 1. Introduction

Majority of patients suffering from coronavirus disease 2019 (COVID-19) caused by severe respiratory syndrome coronavirus-2 (SARS-CoV-2) generally recover from acute infection with least medical interventions [1]. However, clinical progression to severe disease leading to hospitalization causes a considerable impact on patients' health (including morbidity and mortality) and healthcare

systems. Thus, reducing hospitalizations (all-cause or COVID-19-associated) and death remains the most critical component of the ongoing pandemic. From the available medical interventions for COVID-19, vaccination remains the most important tool in reducing the risk of hospitalization and death [1–3]. Few other options are also found to cut this risk if started early, soon after the onset of symptoms [4]. Three monoclonal antibodies (MABs) such as cocktail of casirivimab–imdevimab (REGEN-COV™), and bamlanivimab–etesevimab, and single monoclonal sotrovimab [5–7] have been currently authorized for emergency use (EUA) by the United States Federal Drug Administration (FDA) for the outpatient treatment of mild to moderate COVID-19 in patients  $\geq 12$  years of age (weighing  $\geq 40$  kg) with laboratory-confirmed SARS-CoV-2 infection and, at high risk for progressing to severe COVID-19 and/or hospitalization. Casirivimab (1200 mg) and imdevimab

<sup>☆</sup> **Authorship:** All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship and take responsibility for the integrity of the work. They confirm that this paper will not be published elsewhere in the same form, in English or in any other language, including electronically.

\* Corresponding author. G.D Hospital & Diabetes Institute, Kolkata - 700013, India.

E-mail address: [drawadheshkumarsingh@gmail.com](mailto:drawadheshkumarsingh@gmail.com) (A.K. Singh).

(1200 mg) were authorized to be administered together on November 21, 2020 (the authorized dose was subsequently changed to casirivimab (600 mg) and imdevimab (600 mg). Bamlanivimab (700 mg) and etesevimab (1400 mg) were authorized to be administered together on February 9, 2021. Notably, initially bamlanivimab (700 mg) was authorized for emergency use as monotherapy on November 9, 2020, however the authorization was subsequently revoked on April 16, 2021, due to a sustained increase in variants resistant to bamlanivimab alone resulting in increased risk for treatment failure. Sotrovimab was authorized on May 26, 2021. However, these MAB therapies must be administered by intravenous infusion and/or subcutaneous injection and patients must be monitored through at least 1 h following infusion for purported hypersensitivity (infusion-related reactions including anaphylaxis) reactions. This limits the use of MABs in outpatients setting for the majority of people with COVID-19, compounded further the limited availability of these drugs outside their country of origin and their diminished effectiveness over the emerging newer strains of SARS-CoV-2. A recent study that evaluated the sensitivity of the Delta variant to the humoral immune response found that some MAB targeting the N-terminal and receptor binding domains of the spike protein had impaired binding and neutralization [8]. This suggests that some of these MAB therapies may be less effective to new SARS-CoV-2 variants having mutations in the spike protein [9]. Indeed, bamlanivimab–etesevimab has >45-fold decreased susceptibility against Beta (B.1.351) and >511-fold decreased susceptibility against Gamma (P.1) SARS-CoV-2 variants of concern (VOC) [10,11]. Notably, against new VOC, Omicron (B.1.1.529) neutralizing potency of both bamlanivimab–etesevimab and casirivimab–imdevimab were greatly reduced although sotrovimab has been found to still function with reduced efficacy [12]. Indeed, the only anti-viral drug that has been licensed by FDA is remdesivir for use in both adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. However, remdesivir also require administration by means of infusion or injection in a medical setting with frequent monitoring.

To overcome some of these issues, two new oral anti-viral agents have been recently developed that can be administered by the patient at home shortly after the diagnosis. Both nirmatrelvir plus ritonavir (Paxlovid™ in USA) from Pfizer and molnupiravir (Lageviro™ in USA) from Ridgeback/Merck has received EUA by the USFDA on December 22 and December 23, 2021, respectively, for non-hospitalized adult patients with mild-to-moderate COVID-19. Additionally, molnupiravir has also received restricted use authorization (RUA) from the Central Drugs Standard Control Organization (CDSCO), India on December 28, 2021. These oral agents appear to be an important new weapon for the COVID-19 treatment arsenal. Importantly, while paxlovid™ is currently available in USA, molnupiravir has been made available in majority of countries across the world including India from first week of January 2022.

Aim of this paper is to update our recently conducted systematic review of molnupiravir (data compiled until October 15, 2021) [13] and to provide some practical tips and tricks of using molnupiravir for COVID-19 patients by raising few contemporary questions. Additionally, we also evaluated effectiveness of molnupiravir compared to other drugs having EUA for COVID-19.

## 2. Methods

We searched the electronic data base of PubMed, MedRxiv and Google Scholar to find additional data of molnupiravir that has become available between October 15, 2021, until Jan 5, 2022. We also accessed the data of molnupiravir presented at FDA Antimicrobial Drugs Advisory Committee (AMDAC) meeting on November

**Table 1**  
Results from molnupiravir MOVE-OUT trial in adults with mild-to-moderate COVID-19 [14,21–24].

Outcomes studied	Interim analysis population (7th May – 5th August 2021), m-ITT analysis of 762 participants			Post-interim population (6th August – 2nd October 2021), m-ITT analysis of 646 participants			Full population, m-ITT analysis of 762 + 646 = 1408 participants		
	MOLNU (N = 385); %	PBO (N = 377); %	NNT	MOLNU (N = 324); %	PBO (N = 322); %	NNT	MOLNU (N = 709); %	PBO (N = 699); %	NNT
All-cause hospitalization or death through D29	7.3	14.1	RRR % (95% CI, %); p-value	6.2	4.7	14.7	6.8	9.7	33.9
Hospitalization by D29	7.3	13.8	Risk diff. % (95% CI, %); p-value	NR	NR	NR	6.8	9.6	35.7
Death by day 29	0	2.1	–6.8 (–11.3, –2.4); 0.0024 or 0.0012 <sup>a</sup>	<1	<1	47.6	0.14	1.3	86.2
Covid-related hospitalization or death through D29	6.5	13.3	6.5 (NR)	NR	NR	14.7	6.3	9.2	34.5
			6.8 (NR)						

<sup>a</sup> 1-sided p value; NR: Not reported/retrievable; RRR: Relative risk reduction; MOLNU: Molnupiravir; PBO: Placebo; NNT: Number needed to treat; CI: Confidence interval; m-ITT: Modified-intention-to-treat.

30, 2021. Moreover, we accessed the prescribing information of molnupiravir by FDA (USA), MHRA (UK) and CDSCO (India). Furthermore, we searched the studies conducted with 3 MABs (casirivimab–imdevimab, bamlanivimab–etesevimab, sotrovimab), nirmatrelvir–ritonavir and remdesivir in people with COVID-19.

### 3. Results

We found full published results of phase 3, double-blind, randomized study (MOVE-OUT) that was planned to assess efficacy and safety of molnupiravir in 1433 non-hospitalized adult (18 years or older) participants with COVID-19 (NCT04575597, MK-4482-002) [14]. It should be recalled that an interim analysis ( $n = 775$ ) of MOVE-OUT study that found a significant relative risk reduction of 52% (95% confidence interval [CI], 33 to 80; 1-sided  $p = 0.0012$ ) for hospital admission or death through day 29 was stopped by the independent data safety monitoring board due to excessive benefit in molnupiravir arm compared to the placebo. Intriguingly, in the full results from 1433 participant the relative risk reduction for

hospitalization or death fell to 31% (Hazard ratio [HR] 0.69; 95% CI, 0.48 to 1.01) through day 29 [14]. Another development that took place recently was on November 30, 2021, an FDA advisory panel recommended the agency to grant EUA of molnupiravir in mild to moderate COVID-19 with at least one risk factor by a narrow 13–10 vote margin [15]. FDA announced EUA for molnupiravir on December 23, 2021. To note, Medicines and Healthcare products Regulatory Approval (MHRA) of United Kingdom was the first in the world to conditionally authorize molnupiravir on November 4, 2021, based on interim analysis of MOVE-OUT study [16]. Table 1 summarizes the findings from MOVE-OUT study and FDA AMDAC meeting.

It is important to know, how to use molnupiravir in people with COVID-19. Following questions and answers should help making practical guideline on use of molnupiravir in people with COVID-19.

#### 3.1. What are the prerequisites for EUA/RUA of molnupiravir in COVID-19?

#### Box 1

Summarizes the prerequisites for molnupiravir use in COVID-19 by the FDA, MHRA and CDSCO which are essentially same (difference between three regulators have been highlighted in italics).

##### FDA, USA [17]

EUA of molnupiravir for the treatment of *mild-to-moderate* coronavirus disease 2019 (COVID-19) in adults with positive results of direct SARS-CoV-2 viral testing who are at high risk for progressing to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate subject to following conditions:

1. Molnupiravir may only be prescribed for an individual patient by *physicians, advanced practice registered nurses, and physician assistants* that are licensed or authorized under state law to prescribe drugs in the therapeutic class.
2. The recommended dose should be 800 mg twice daily for 5 days with or without food.
3. Molnupiravir is not authorized -i. For use in patients less than 18 years of age
- ii. For initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19.
- iii. For use for longer than 5 consecutive days.
- iv. For pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- v. For pregnant women.
- vi. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
- vii. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

##### CDSCO, India [18]

Molnupiravir for restricted use under emergency situation in the country for treatment of adult patients with COVID-19, *with SpO<sub>2</sub> ≥93%*, and who have high risk of progression of disease including hospitalization or death and for whom alternative COVID-19 treatment options authorized by CDSCO are not accessible or clinically appropriate subject to following conditions:

1. The drug should be sold by retail only under prescription of *medical specialists*.
2. The recommended dose should be 800 mg twice daily for 5 days with or without food.
3. Molnupiravir is not authorized – i. For use in patients less than 18 years of age.
- ii. For initiation of treatment in patients requiring immediate hospitalization due to COVID-19 at that stage, (however, if it was initiated before hospitalization due to COVID 19, it may be continued).
- iii. For use for longer than 5 consecutive days.
- iv. For pre-exposure or post-exposure prophylaxis for prevention of COVID-19.
- v. For pregnant women.
- vi. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
- vii. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.

##### MHRA, UK [16,19]

1. Patients must fulfil *ALL* eligibility criteria to receive it. a. SARS-CoV-2 infection is confirmed by PCR testing within the last 5 days, AND b. Onset of symptoms of COVID-19 within the last 5 days, AND c. *A member of a 'highest' risk group*

"Highest risk" group include: a. Patients with active cancer

b. Patients with a hematological diseases and stem cell transplant recipients

c. Patients with renal disease

d. Patients with liver disease

e. Patients with immune-mediated inflammatory disorders

f. Primary immune deficiencies

g. HIV/AIDS

h. Solid organ transplant recipients

i. Rare neurological conditions

j. All patients with Down's syndrome

2. Patients who should not receive molnupiravir include: a. Those who do not fulfil ALL inclusion criteria

b. Those who are allergic to molnupiravir or any of the other ingredients of this medicine

c. Children less than 18 years as there is insufficient data

• During pregnancy and breastfeeding as there is insufficient data

**Box 2****Criteria to identify high risk individuals with COVID-19**

*High risk cases included in molnupiravir study (MOVE-OUT) High risk cases recognized by CDC for monoclonal antibodies EUA [20]*

- |   |   |
|---|---|
| <p>[14]</p> <ul style="list-style-type: none"> <li>a. People with &gt;60 years of age,</li> <li>b. Active cancer,</li> <li>c. Chronic kidney diseases (CKD),</li> <li>d. Chronic obstructive pulmonary diseases (COPD),</li> <li>e. Obesity (body mass index [BMI] <math>\geq 30</math> kg/m<sup>2</sup>),</li> <li>f. Serious heart conditions (coronary artery diseases [CAD], heart failure, cardiomyopathies),</li> <li>g. Diabetes mellitus</li> </ul> <p>MHRA, UK included “highest risk” for molnupiravir EUA as follows:</p> <ul style="list-style-type: none"> <li>a. Patients with active cancer</li> <li>b. Patients with a hematological diseases and stem cell transplant recipients</li> <li>c. Patients with renal disease</li> <li>d. Patients with liver disease</li> <li>e. Patients with immune-mediated inflammatory disorders</li> <li>f. Primary immune deficiencies</li> <li>g. HIV/AIDS</li> <li>h. Solid organ transplant recipients</li> <li>i. Rare neurological conditions</li> <li>j. All patients with Down's syndrome</li> </ul> | <ul style="list-style-type: none"> <li>a. Older age (for example, age <math>\geq 65</math> years of age)</li> <li>b. Obesity or being overweight (BMI <math>&gt;25</math> kg/m<sup>2</sup>)</li> <li>c. Chronic kidney disease</li> <li>d. Diabetes</li> <li>e. Immunosuppressive disease or immunosuppressive treatment</li> <li>f. Cardiovascular diseases (including congenital heart disease) or hypertension</li> <li>g. Chronic lung diseases (chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)</li> <li>h. Sickle cell disease</li> <li>i. Neurodevelopmental disorders (cerebral palsy) or other conditions that confer medical complexity (genetic or metabolic syndromes and severe congenital anomalies)</li> <li>j. Having a medical-related technological dependence (tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))</li> </ul> |
|---|---|

**Box 3****Definition of mild and moderate COVID-19 as per FDA [14,17].****Mild COVID-19**

Upper respiratory tract symptoms and or fever without shortness of breath or hypoxia

**Moderate COVID-19**

(a) Shortness of breath with exertion, respiratory rate  $\geq 20$  to  $<30$  breaths per min, and/or heart rate  $\geq 90$  to  $<125$  beats per minute AND,  
 (b) SpO<sub>2</sub>  $>93\%$  on room air or on supplemental oxygen (which has not increased since onset of COVID-19 signs/symptoms) for a reason other than COVID-19 (or patient was receiving  $\leq 4$  L/min supplemental oxygen for COVID-19, regardless of SpO<sub>2</sub>, but was not previously on supplemental oxygen) AND,  
 (c) No shortness of breath at rest, respiratory failure, shock, or multi-organ dysfunction/failure.

**3.2. Who are at risk to progress to severe COVID-19 where molnupiravir has been given EUA/RUA?**

Those who are at risk to progress to severe COVID-19 has been summarized in Box 2. FDA recognized high risk cases similar for molnupiravir EUA as that for monoclonal antibodies EUA provided by Centre of Disease Control (CDC), USA. For MHRA, UK, “highest risk” cases are closely similar. Notably, following risk factors have been chosen as inclusion criteria in MOVE-OUT study. Importantly, authorization of REGEN-COV™ under the EUA is not limited to medical condition or factors listed below. CDSCO has followed FDA risk category.

**3.3. What is the definition of mild-to-moderate COVID-19 where molnupiravir has been given EUA by FDA?**

FDA has given EUA to molnupiravir in adults with mild-to-moderate COVID-19 with risk factors based on certain criteria while CDSCO, India recommend molnupiravir to adults having COVID-19 with risk factors for severity and oxygen saturation (SpO<sub>2</sub>)  $>93\%$ . Box 3 summarizes the FDA definition of mild-to-moderate COVID-19.

**3.4. What are administrative instructions for molnupiravir?**

- a. Inform patients to take molnupiravir 800 mg twice daily for 5 days, with or without food.
- b. Advise patients to swallow molnupiravir capsules whole, and to not open, break, or crush the capsules.
- c. Instruct patients that if they miss a dose of molnupiravir and it is within 10 h of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 h, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose [17,18].

**3.5. Are dose modifications required in elderly, obese and people with kidney and liver diseases?**

No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients. In MOVE-OUT study, there was no difference in safety and tolerability between patients  $\geq 65$  years of age and younger patients who were treated with



**Box 4**

Preclinical studies with molnupiravir [23,24].

Types of preclinical Study	Kinds of study	Results
<i>in vitro</i>	Regulatory bacterial mutagenicity assay (Ames)	Positive
	Regulatory human lymphoblastoid TK6 cells micronucleus study	Negative
<i>in vivo</i>	Non-regulatory Chinese hamster cells (CHO) 32-day assay	Positive
	Rat micronucleus study	Negative
	Pig-a (28-day rat study)	Equivocal
	Transgenic (Big Blue) 28-day rat study (Gold standard)	Negative
Animal studies (Hematopoietic system)	1-month dog study	Pancytopenia and bone marrow depletion after $\geq 2$ -weeks of exposure
	12-week rat study	No effect on hematopoietic system
	4-week mice study	No effect on hematopoietic system
	2-week rabbit study	No effect on hematopoietic system
	1-week nonhuman primates' study	No effect on hematopoietic system
Animal studies (Bone and cartilage)	1-month studies on mice, rats or dogs	No effect on growth plates
	3-month rat study	Dose-dependent increased thickness of growth plate in rapidly growing mice

molnupiravir. No dosage adjustment is recommended based on age and BMI. Since renal clearance is not a meaningful route of elimination for N-hydroxycytidine (NHC, active form of molnupiravir), no dosage adjustment is required in patients with any degree of renal impairment. Data suggest mild or moderate renal impairment did not have a meaningful impact on the pharmacokinetics (PK) of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73 m<sup>2</sup> or on dialysis and severe renal impairment, people with end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure. Similarly, preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination and therefore hepatic impairment is unlikely to affect NHC exposure [17,18].

### 3.6. What are the warnings, precautions, and contraindications of molnupiravir?

There is limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use. No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under EUA. Molnupiravir is not recommended for use during pregnancy because of embryo-fetal toxicity observed in preclinical animal studies. Similarly, molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth observed in preclinical animal studies [17,18].

### 3.7. Is there any food or drug-to-drug interaction of molnupiravir?

Molnupiravir can be taken orally with or without food. No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir authorized under EUA. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted [17,18].

### 3.8. Can we use molnupiravir in pregnancy and lactating mothers?

The use of molnupiravir is not recommended during pregnancy. When considering molnupiravir for a pregnant individual,

the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using molnupiravir during pregnancy to the pregnant individual. Molnupiravir may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual. It should be recalled that there are maternal and fetal risks associated with untreated COVID-19 in pregnancy. There are no data on the presence of molnupiravir or its metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir however, it is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production. Based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir [17,18].

### 3.9. Any advice required for women or men receiving molnupiravir planning for pregnancy?

- Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
- Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose. While the risk is regarded as low, nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. The risk beyond three months after the last dose of molnupiravir is unknown and studies to understand the risk beyond three months are ongoing [17,18].

### 3.10. What are the most common adverse reaction seen with molnupiravir?

Most common (incidence  $\geq 1\%$ ) adverse reactions observed are diarrhea, nausea, and dizziness but it is similar to placebo [17,18].

### 3.11. Was any adverse event of special interest noted in clinical trials of molnupiravir?

Since significant bone marrow toxicity was reported in a 28-day toxicology study in dogs, this finding prompted a careful assessment of hematologic parameters in clinical trials. A decrease in hemoglobin was observed in molnupiravir arm both in MOVE-OUT and MOVE-IN study. Hemoglobin laboratory abnormalities that were a worsened grade from baseline were more common among molnupiravir participants than placebo. Grade 1 and 2 hemoglobin decreased abnormalities (8.5–10.4 g/dL in females and 9.0–10.9 g/dL in males) were reported in 4% and 1% of the molnupiravir and placebo arms, respectively. Hemoglobin abnormalities (any grade but predominantly Grade 1 and 2 in severity) were reported in 22.4% of participants receiving molnupiravir 800 mg compared to 8.3% of participants receiving placebo in MOVE-IN study. However, this hematological abnormality was not considered clinically meaningful [21,22].

### 3.12. Why FDA gave EUA of molnupiravir despite some concern in preclinical studies?

Box 4 summarizes the findings from genotoxicity studies. Studies evaluating embryo-fetal lethality and teratogenicity in rats and rabbits showed harm on 3-to-18-fold higher NHC exposure and based on these findings molnupiravir is not recommended in pregnancy. Based on all preclinical studies FDA review committee observed that [21–23]:

- The comprehensive genotoxicity assessments in robust and well-characterized regulatory studies indicate molnupiravir has low risk for genotoxicity.
- Hematopoietic findings, observed in dogs only, were not seen clinically meaningful in molnupiravir studies.
- Growth plate findings in rapidly growing rats administered molnupiravir for 3 months are not relevant for adults.
- Embryo-fetal lethality and teratogenicity was observed in pregnant rats at 8-fold of clinical NHC exposure, and not observed in rabbits until 18-fold of the NHC clinical exposure.

- There were no molnupiravir-related effect on growth, sexual maturation, neurobehavioral, or reproductive function in the offspring observed in preliminary pre- and post-natal development (PPND) study results (in pregnant rats at ~2-fold the clinical NHC exposure).

Based on the findings in rats, use of molnupiravir during pregnancy is not recommended and use of contraception in individuals of child-bearing potential is advised for the duration of NHC systemic exposure (during treatment and for the 4 days following completion).

### 3.13. Why effectiveness to reduce hospitalization or death by nearly 50% observed during the interim analysis of MOVE-OUT study of molnupiravir fell down to nearly 30% after the full completion of the trial?

The incidence of hospitalization or death in modified intention-to-treat (m-ITT) interim analysis of both interim (7.3 vs. 14.1% in molnupiravir vs. placebo, respectively) and all-randomized participants (6.9 vs. 9.7% in molnupiravir vs. placebo, respectively) were consistent in the molnupiravir group vs. placebo but fell in the post interim population of placebo arm (6.2 vs. 4.7% in molnupiravir vs. placebo, respectively) compared to the placebo group of interim population (Table 1). While the exact reasons for this difference in outcome are unknown, potential contributing factors may include-baseline imbalances in the two arms, regional variations in the severity of enrolled participants and different hospitalization practices and shifts in the epidemiology of the COVID-19 pandemic amongst newly enrolling participating countries. Indeed, in the interim analysis sample, more women were randomly assigned to molnupiravir (difference, 7.6%) than in the all-randomized sample (difference, 4.7%). However, more female patients (purportedly who have a lower risk of severe COVID-19 than male patients), more participants with SARS-CoV-2 nucleocapsid antibodies suggestive of recent or past infection (suggests a lower risk), and more participants with low viral load at baseline (in whom there is less virologic effect) were recruited in the placebo group of all-randomized sample compared to the interim analysis sample (Table 2). All these factors may have contributed to a lower overall event rate in the placebo group in the all-randomized sample than in the interim analysis [14]. Moreover, the interim results showed eight deaths in the placebo group and none in the molnupiravir group, while the post-interim results showed one death in each group. When questioned why the trial's later participants showed

**Table 2**  
Imbalance in baseline characteristics in interim analysis and all-population analysis group [14,21–24].

Characteristics	Interim analysis sample			Full-population analysis sample			Difference in PBO arm $\Delta$ (Full-population – Interim population)
	MOLNU	PBO	$\Delta$ (MOLNU - PBO)	MOLNU	PBO	$\Delta$ (MOLNU - PBO)	
Female (%)	51.7	44.1	7.6	53.6	49.0	4.6	4.9
Male (%)	48.3	55.9	-7.6	46.4	51.0	-4.6	-4.9
Age $\leq 60$ Yrs. (%)	86.8	85.8	1.0	83.4	82.3	1.1	-3.5
Age $> 60$ Yrs. (%)	13.2	14.2	-1.0	16.6	17.7	-1.1	3.5
Mean age (Yrs.)	43.2	44.2	-1.0	44.4	45.3	-0.9	1.1
Median age (Yrs.)	41.0	43.0	-2.0	42.0	44.0	-2.0	1.0
Asian (%)	1.8	2.8	-1.0	3.6	3.2	0.4	0.4
Europe (%)	23.0	23.2	-0.2	32.1	33.3	-1.2	10.1
Diabetes (%)	12.4	14.7	-2.3	14.9	16.9	-2.0	2.2
Delta (%)	35.1	33.0	1.9	33.1	31.1	2.0	-1.9
Low viral load <sup>a</sup> (%)	22.5	19.8	2.7	22.5	22.7	-0.2	2.9
Baseline NCAB positive (%)	18.3	18.0	0.3	19.1	20.5	-1.4	2.5

<sup>a</sup> Low viral load was defined as  $\leq 10^6$  copies/mL; MOLNU: Molnupiravir; PBO: Placebo; NCAB: Nucleocapsid antibody.

such different outcomes than those in the interim analysis, a physician representing Merck told the panelists that the post-interim group contained older patients, were more likely to be female and recruited from Europe, and more likely to carry the delta variant [25]. Notably, the proportion of patients requiring hospitalization or death through day 29 were higher in molnupiravir vs. placebo (6.2% vs. 4.7%, respectively) in post-interim group compared with interim group analysis where proportion of patient requiring hospitalization or death through day 29 were lower in molnupiravir vs. placebo (7.3% vs. 14.1%, respectively) group. These heterogeneity in outcomes appeared to be the reason of diminished effectiveness in all-population analysis. It should be noted that while composite of hospitalization or death decreased to nearly 30%, a relative risk reduction of 89% (95% CI, 14%–99%) in death through day 29 were noted in molnupiravir arm compared to placebo in full analysis (Table 1).

### 3.14. Is effectiveness of molnupiravir similar in all adult patients with mild-to-moderate COVID-19?

In most prespecified subgroups, the percentage of participants who were hospitalized or died were lower with molnupiravir than placebo, however the accompanying confidence interval indicates substantial uncertainty about the magnitude of these effects. Moreover, molnupiravir was not effective (the point estimate for the difference in the risk of hospitalization or death through day 29 was favored for placebo over molnupiravir) [14] –

- In patients with SARS-CoV-2 nucleocapsid antibodies at baseline,
- Patients with low viral load at baseline,
- Patients with diabetes at baseline,
- Patients who identified themselves as Asian only, Black only, Native American only, or mixed Black–Native American–White,
- Patients enrolled in the Asia-Pacific region.

Caveat for these subgroups who had no benefit with molnupiravir was based on small sample size, lesser number of events with imprecise (fairly wide) point estimates when associated 95% confidence intervals included zero (Table 3).

### 3.15. Is molnupiravir effective in people with breakthrough SARS-CoV-2 infection (post vaccination) or in people with past history of SARS-CoV-2 infection?

Vaccination status could be considered as one of the potential patient selection criteria. Vaccinated individuals were excluded from MOVE-OUT study (MK-4482-002), thus effect of molnupiravir

in breakthrough infections is not known. Since the risk of hospitalization and death among fully vaccinated individuals is known to be significantly lower than the risk among unvaccinated individuals, role of molnupiravir is expected to be limited and hence should be avoided in our opinion unless benefit to risk ratio is in favor of molnupiravir. No significant effect of molnupiravir in reducing hospitalization or death in people who had positive nucleocapsid antibody (20% at baseline) suggestive of recent or past SARS-CoV-2 infection, suggests avoiding its use unless benefit to risk ratio is in favor of molnupiravir.

### 3.16. Is molnupiravir effective in all VOC of SARS-CoV-2 including omicron?

55% of samples of confirmed COVID-19 from the molnupiravir MOVE-OUT study were sequenced, of which 58% had Delta (B.1.617.2), 20% had Mu (B.1.621), 11% had Gamma (P.1) and 3% each were of Alpha and Lambda strain. 44% had missing sequence data. Subgroup analysis found molnupiravir was effective irrespective of strain although no data is available for its effect on Omicron in particular [14]. Unlike MABs, the mechanism of action of molnupiravir is independent of mutations in the spike protein, and thus it is expected to work against Omicron, theoretically [26]. Indeed, *in vitro* study of VeroE6-GFP cells does indicate that molnupiravir retain their activity against the VOCs of Alpha, Beta, Gamma, Delta, and Omicron but no clinical studies yet available to indicate effectiveness of molnupiravir in people infected with omicron [27].

### 3.17. How is molnupiravir effectiveness in comparison to other EUA approved drugs in COVID-19?

All 3 MABs, remdesivir, nirmatrelvir plus ritonavir and molnupiravir have been studied in mild-to-moderate COVID-19 against placebo [28–32]. Table 4 summarizes the comparative efficacy of all these drugs. Notably, these are not head-to-head studies comparing these agents and primary objective were slightly different. For example–primary outcome was all-cause hospitalization or death for molnupiravir (MOVE-OUT), nirmatrelvir-ritonavir (EPIC-HR) and sotrovimab (COMET-ICE) while it was COVID-19-related hospitalization or death for casirivimab–imdevimab (REGEN-COV), bamlanivimab–etesevimab (BLAZE-1) and remdesivir (PINETREE). Number needed to treat (NNT) to prevent 1 hospitalization (all-cause or COVID-19-related) or death from these 6 drugs varied from 18 (nirmatrelvir-ritonavir) to 34 (molnupiravir). Similarly, NNT for reducing 1 death varied from 53 (bamlanivimab–etesevimab) to 265 (sotrovimab). NNT for reducing 1 death for molnupiravir was 85 whereas it was 91 for nirmatrelvir-ritonavir. NNT for death alone was not calculable for remdesivir (no death took place in either arm, in

**Table 3**

Subgroups who appeared to have no benefit in hospitalization or death through day 29 with molnupiravir over placebo [14,21–24].

		Interim analysis, absolute risk difference (%; 95% CI)	Full-analysis population, absolute risk difference (%; 95% CI)
Diabetes at baseline	Yes	–4.5 (–20.1, 11.8)	1.4 (–8.2, 11.1)
	No	–6.8 (–11.4, –2.5)	–3.6 (–6.6, –0.7)
Baseline nucleocapsid antibody status	Positive	0 (–7.5, 7.3)	2.3 (–1.7, 7.1)
	Negative	–9.4 (–14.9, –4.1)	–5.1 (–8.8, –1.6)
Race	Asian only	NR	0.7 (not calculated)
	Black only	NR	4.8 (–8.3, 18.0)
	Native Americans only	NR	4.7 (–8.4, 16.5)
	Mixed	NR	3.6 (–8.1, 15.5)

NR: Not reported/retrievable, CI: Confidence interval.



**Table 4**  
Comparative efficacy data of EUA/authorized<sup>#</sup> drugs for COVID-19 [14,28–32].

	Bamlanivimab–Etesevimab* (BLAZE-1) <sup>28</sup> N = 1,035	Casirivimab–Imdevimab* (REGEN- COV <sup>TM</sup> ) <sup>29</sup> N = 1,484 <sup>^</sup>	Sotrovimab (COMET- ICE) <sup>30</sup> N = 1,057	Nirmatrelvir–Ritonavir (EPIC-HR) <sup>31</sup> (N = 2,246)	Molnupiravir (MOVE-OUT) <sup>14</sup> N = 1,433	Remdesivir <sup>##</sup> (PINETREE) <sup>32</sup> N = 562
<b>Primary outcome: hospitalization or death, through Day-29 (BLAZE-1, REGEN-COV, COMET-ICE and MOVE-OUT) or Day-28 (EPIC-HR and PINETREE)</b>						
Drug initiation, time from symptom onset (day)	3	10	5	5	5	7
Active arm event, n/N (%)	11/518 (2.1%)*	7/736 (1.0%)*	6/528 (1.1%)	8/1039 (0.77%)	48/709 (6.77%)	2/279 (0.7%)*
Placebo arm event, n/N (%)	36/517 (7%)*	24/748 (3.2%)*	30/529 (5.7%)	66/1046 (6.3%)	68/699 (9.72%)	15/283 (5.3%)*
Absolute risk difference % (95% CI), P-value	4.8%* (–7.4 to –2.3)	2.2%*	4.6%	5.5%, P < 0.0001	3.0% (–5.9 to –0.1), 1-side P = 0.0218	4.6%*
Hazard ratio (95% CI), P-value	NR	NR	0.21 (0.09–0.50), P < 0.001	0.12	0.69 (0.48–1.01)	0.13* (0.03–0.59), P = 0.008
Relative risk reduction (95% CI), P-value	70%*, P < 0.001	70.4%* (31.6–87.1), P = 0.002	79% (50–91), P < 0.001	88%	31.0% (1–52)	87%*
NNT	20.4*	45.5*	21.7	18	33.9	21.7*
<b>Death</b>						
Active arm event, n/N (%)	0/518 (0%)	1/736 (0.14%)	0/528 (0%)	0/1039 (0%)	1/709 (0.14%)	0/279 (0%)
Placebo arm event, n/N (%)	10/517 (1.9%)	1/748 (0.13%)	2/529 (0.37%)	12/1046 (1.1%)	9/699 (1.3%)	0/283 (0%)
Absolute risk difference	1.9%	0.08%	0.37%	1.1%	1.16%	NA
Hazard ratio (95% CI)	NA	NA	NA	NA	0.109	NA
Relative risk reduction	NA	–1.6% (–1522, 93.6)	NA	NA	89.1%	NA
NNT	52.6	–10,000 (NNH)	265	91	86.2	NA
Working or expected to work against omicron <sup>8–12,27</sup>	No	No	Yes, but with reduced efficacy	? Yes ( <i>in vitro</i> study)	? Yes ( <i>in vitro</i> study)	? Yes ( <i>in vitro</i> study)
Cost of one full course (US, INDIA)	USD: 2400 INDIA: NA	USD: 2100 INR: 60,000–78,000	USD: 2100 INDIA: NA	USD: 530 INDIA: NA	USD: 700 INR: 1,400–3,000	USD: 1,872 INR: 3,600–14,000

\* Primary outcome was COVID-19-related hospitalization or death; <sup>^</sup> Data for 1200-mg dose; NNT: Number needed to treat; NNH: Number needed to harm; NA: Not available/applicable; CI: Confidence interval; EUA: Emergency use authorization; USD: US Dollar; INR: Indian Rupees; CI: Confidence interval, EUA: Emergency use authorization; BLAZE-1: Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies; COMET-ICE: The COVID-19 Monoclonal antibody Efficacy Trial-Intent to Care Early; EPIC-HR: Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients; MOVE-OUT: Efficacy and safety of molnupiravir (MK-4482) in non-hospitalized adult participants with COVID-19 (MK-4482-002); PINETREE: Study to evaluate the efficacy and safety of remdesivir (GS-5734<sup>TM</sup>) treatment of COVID-19 in an outpatient setting.

**Box 5****Practical Guideline for use of molnupiravir in confirmed COVID-19 patients in India***Essential criteria as per CDSCO*

- a. Adults (>18 years) AND,
- b. Non-pregnant AND,
- c. SpO<sub>2</sub> >93% on room air AND,
- d. Having ≥1 risk factors for progression to severe COVID-19 (Box 2) AND, e. Within 5-days of symptoms

*Recommendation*

- a. 800 mg twice daily for 5 days with or without food
- b. No dose adjustment required for elderly, obese, CKD, chronic liver disease
- c. Females: having childbearing potential to use a reliable method of contraception during entire duration of treatment and for 4 days after the last dose of molnupiravir.
- d. Males: having reproductive potential and are sexually active with females of childbearing potential to use a reliable method of contraception during treatment and for at least 3 months after the last dose of molnupiravir.
- e. Enquire about vaccination status and assess risk vs. benefit of using molnupiravir in fully vaccinated individuals
- f. Enquire about past SARS-CoV-2 infection and assess risk vs. benefit of using molnupiravir in people with confirmed recent past history.

PINETREE study). Contrarily, no reduction in death over placebo and a very rare possibility of harm (NNH = 10,000) cannot be rule out with casirivimab–imdevimab.

### 3.18. What other safety concern of molnupiravir observed in clinical studies are not fully settled yet?

Treatment-emergent amino acid changes and spike mutation rates were analyzed from the clinical studies (MK-4482-001 and MK-4482-002, Part 1) that evaluated molnupiravir against placebo [21–24]. A significantly higher nucleotide mutation rate was observed with molnupiravir which is consistent with its mechanism of action (MOA). Although there was an increase in nucleotide changes of all types, most of the mutations observed were transition mutations consistent with the MOA of molnupiravir. Similarly, a greater proportion of molnupiravir participants had at least one treatment-emergent amino acid substitution or other structural nucleotide change (deletion, insertion) in the spike gene compared to the placebo which is again consistent with the MOA of molnupiravir. Collectively, these analyses indicates that molnupiravir treatment may increase the rate of emergence of SARS-CoV-2 with amino acid changes in the viral spike protein, consistent with its mutagenic MOA. However, at the individual patient level – a. there was no evidence that the emergence of spike amino acid changes has affected the virologic or clinical outcomes in outpatients with COVID-19 such as in MOVE-OUT study, b. the transmissibility of variants arising is likely to be quite low, c. most spike protein changes was of minority variants, d. antiviral activity of molnupiravir will likely accelerates the viral clearance and, e. even in the absence of an antiviral effect of molnupiravir, overall viral shedding will be likely rapidly declining by the time a treatment-emergent spike amino acid variant emerges. Nonetheless, many uncertainties still remain regarding these findings from the clinical and public health perspective especially when we anticipate a widespread use of molnupiravir globally.

## 4. Conclusions

Collectively, from the available evidence currently available, molnupiravir appears to be reasonably useful agent in reducing death and composite of hospitalization or death in adult patients with COVID-19 having high risk, with a relatively lower cost. These findings are very important in the context of India, where only 2 other agents (casirivimab–imdevimab and remdesivir) are currently available to be used in patients with COVID-19 having high risks. Both remdesivir and casirivimab–imdevimab requires hospital admission for infusion administration and need

subsequent monitoring. Casirivimab–imdevimab are ineffective against Omicron variant. Therefore, role of molnupiravir cannot be undermined especially when it can be used in out-patient settings through oral route with a lower cost and its likely effectiveness against the Omicron variant. Nevertheless, it should also be remembered that there is no data of molnupiravir effectiveness in vaccinated people having breakthrough infections, and outcomes in people having past history of SARS-CoV-2 infection (positive nucleocapsid antibody) is not better when compared with placebo. These points are of considerable importance in country like India where nearly half of population are 2-dose vaccinated and more than two-third had past history of SARS-CoV-2 infection, as per the last serosurvey. Therefore, role of molnupiravir is expected to be limited. Finally, while short-term use of 5-days is unlikely to have any long-term major concern on individual patient level, inappropriate and injudicious use in too many individuals without assessing risk: benefit ratio may pose an unknown long-term risk of theoretical public concern. Thus, use molnupiravir carefully and judiciously. Box 5 summarizes some useful tips and tricks of using molnupiravir in non-pregnant adult patients with COVID-19 with high risk for severity including hospitalization.

## Funding

No funding.

## Author's contribution

AKS conceptualized, searched the literature; AKS and AS conducted the statistical calculation; AS and RS wrote the first draft; AKS, AS, RS and AM edited the final draft. All authors agreed mutually to submit for publication.

## Declaration of competing interest

We hereby declare that we have no conflict of interest, related to this article titled “An Updated Practical Guideline on Use of Molnupiravir and Comparison with Agents having Emergency Use Authorization for Treatment of COVID-19”.

## References

- [1] Tenforde MW, Kim SS, Lindsell CJ, et al. 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, March–June 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:993–8.
- [2] Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 cases and hospitalizations among adults, by vaccination status — New York, May 3–July

- 25, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1306–11.
- [3] Bajema KL, Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA vaccines against COVID-19-associated hospitalization — five veterans affairs medical centers, United States, February 1–August 6, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1294–9.
- [4] Hurt AC, Wheatley AK. Neutralizing antibody therapeutics for COVID-19. *Viruses* 2021;13:628.
- [5] Horby PW, Mafham M, Peto L, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. June 16, 2021.
- [6] Gottlieb RL, Nirula A, Chen P, et al. 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;325:632–44.
- [7] Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med* 2021;385:1941–50.
- [8] Planas D, Veyer D, Baidaliuk A, Staropoli I, Guivel-Benhassine F, Rajah MM, et al. Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization. *Nature* 2021 Aug 12;596:276–80.
- [9] European Centre for Disease Prevention and Control. Risk assessment: SARS-CoV-2 - increased circulation of variants of concern and vaccine rollout in the EU/EEA, 14th update. Stockholm (Sweden): European Centre for Disease Prevention and Control (ECDC); 2021 Feb 15.
- [10] US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of bamlanivimab and etesevimab. Available at: <https://www.fda.gov/media/145802/download>. [Accessed 5 January 2022].
- [11] US Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of REGEN-COV (casirivimab with imdevimab). Available at: <https://www.fda.gov/media/145611/download>. [Accessed 5 January 2022].
- [12] Cao Y, Wang J, Jian F, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *bioRxiv preprint doi: <https://doi.org/10.1101/2021.12.07.470392>*; this version posted December 22, 2021.
- [13] Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. *Diabet Metab Syndr* 2021;15(6):102329.
- [14] Jayk Bernal A, da Silva MMG, Musungaie DB, et al. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med* 2021 Dec 16. <https://doi.org/10.1056/NEJMoa2116044>. *NEJMoa2116044*, [Online ahead of print].
- [15] FDA okays emergency use of molnupiravir pill for COVID-19 (medscape.com) Accessed on Jan 5, 2022.
- [16] Regulatory approval of Lagevrio (molnupiravir) - GOV.UK. [www.gov.uk](http://www.gov.uk). [Accessed 5 January 2022]. <https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/patient-information-leaflet-for-lagevrio>.
- [17] Fact sheet for healthcare providers: emergency use authorization for molnupiravir (fda.gov). 2022. January 5.
- [18] Fact sheet for healthcare professionals: restricted emergency use for molnupiravir in India (prescribing information for molcovir by Optimus pharma).
- [19] (england.nhs.uk), C1530\_Interim-clinical-commissioning-policy-neutralising-mono-clonal-antibodies-or-antivirals-for-non-hospitali.pdf. [Accessed 5 January 2022]. [https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/12/C1530\\_Interim-clinical-commissioning-policy-neutralising-mono-clonal-antibodies-or-antivirals-for-non-hospitali.pdf](https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/12/C1530_Interim-clinical-commissioning-policy-neutralising-mono-clonal-antibodies-or-antivirals-for-non-hospitali.pdf).
- [20] Centers for Disease Control and Prevention. People at increased risk: and other people who need to take extra precautions. <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html>. [Accessed 5 January 2022].
- [21] U.S. Food and Drug Administration. In: Center for drug evaluation and research FDA briefing document antimicrobial drugs advisory committee meeting; November 30, 2021. <https://www.fda.gov/media/154418/download>. [Accessed 5 January 2022].
- [22] Center for drug evaluation and research antimicrobial drugs advisory committee meeting briefing document molnupiravir oral treatment of COVID-19 APPLICATION NUMBER: EUA #000108. <https://www.fda.gov/media/154421/download>. [Accessed 5 January 2022].
- [23] FDA introductory remarks. In: Antimicrobial drugs advisory committee meeting; November 30, 2021. <https://www.fda.gov/media/154473/download>. [Accessed 5 January 2022].
- [24] Molnupiravir. In: Merck presentation at USFDA antimicrobial drugs advisory committee meeting; November 30, 2021. <https://www.fda.gov/media/154472/download>. [Accessed 5 January 2022].
- [25] Dyer O. Covid-19: FDA expert panel recommends authorising molnupiravir but also voices concerns. *BMJ* 2021;375:n2984. <https://doi.org/10.1136/bmj.n2984>.
- [26] Merck and pfizer COVID-19 pills effective against omicron -U.S. FDA official | reuters. Accessed January 5, 2022.
- [27] Vangeel L, Jonghe SD, Maes P, et al. Remdesivir, Molnupiravir and Nirmatrelvir remain active against SARS-CoV-2 Omicron and other variants of concern. *bioRxiv preprint doi: <https://doi.org/10.1101/2021.12.27.474275>*; posted December 28, 2021.
- [28] Dougan M, Nirula A, Azizad M, et al. Bamlanivimab plus etesevimab in mild or moderate covid-19. *N Engl J Med* 2021;385:1382–92. <https://doi.org/10.1056/NEJMoa2102685>.
- [29] Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV antibody combination and outcomes in outpatients with covid-19. *N Engl J Med* 2021;385:e81. <https://doi.org/10.1056/NEJMoa2108163>.
- [30] Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of the neutralizing SARS-CoV-2 antibody sotrovimab in preventing progression of COVID-19: a randomized clinical trial. *medRxiv preprint doi: <https://doi.org/10.1101/2021.11.03.21265533>*; posted November 8, 2021.
- [31] Pfizer announces additional phase 2/3 study results confirming robust efficacy of novel COVID-19 oral antiviral treatment candidate in reducing risk of hospitalization or death | pfizer. Accessed January 5, 2022.
- [32] Gottlieb RL, Vaca CE, Paredes R. Early remdesivir to prevent progression to severe covid-19 in outpatients. published on December 22, 2021, at *NEJM.org*. DOI: 10.1056/NEJMoa2116846.