Molnupiravir - the First Oral Antiviral for COVID-19: A Literature Review

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Abstract

The COVID-19 pandemic is still an unresolved global health concern, although half of the world's population has been vaccinated. The pharmaceutical industries are still struggling to develop effective antivirals against SARS-CoV-2. Molnupiravir is a new oral antiviral with antiviral properties by targeting coronavirus RNA. This literature review aims to describe the mechanism of action, efficacy, and safety of molnupiravir based on published preclinical and clinical studies for COVID-19 treatment. Relevant studies were collected by electronic databases, including Google Scholar, PubMed, and Science Direct. The inclusion criteria were preclinical and clinical trials related to molnupiravir as an antiviral for the COVID-19 treatment published in December 2019 to January 2022. Preclinical trials demonstrated therapeutic and prophylactic properties against SARS-CoV-2 in cell culture and animal models. Molnupiravir is currently under the emergency use authorization from the FDA to treat COVID-19. Its potent and broad antiviral activity is demonstrated through a mechanism of error catastrophe that causes coronavirus RNA mutagenesis. The published clinical trials have shown that molnupiravir is well-absorbed, well-tolerated, and has relatively mild side effects such as headache, nausea, and diarrhea with a minimal incidence at a dose of 800 mg twice daily. Time to viral RNA clearance was significantly decreased in patients administered molnupiravir 800 mg compared to those who administered placebo (14 days vs 15 days, *P* value=0,013). Molnupiravir is a promising oral antiviral that can reduce the incidence of COVID-19 hospitalization or death. Further clinical trials regarding its efficacy for severe symptoms and other clinical aspects such as drug interactions and contraindications are still needed.

Keywords: Molnupiravir/EIDD-2801, SARs-CoV-2, COVID-19, Oral Antiviral, Clinical Efficacy

INTRODUCTION

Although adequate vaccines are currently available to prevent severe COVID-19 and the development of new vaccines is ongoing, effective antiviral therapies for SARS-CoV-2 are still lacking. Several antivirals have received Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) to treat COVID-19, but their use is limited in a hospital setting. The need for oral antiviral has become a major priority since the pandemic outbreak to make it consumable to outpatients (Fan et al., 2021; Singh et al., 2021[a]). Towards the end of 2021, Food and Drug Administration US declared EUAs of two new oral antivirals for high-risk, non-hospitalized patients with mild to moderate COVID-19 symptoms. These antivirals are ritonavir-boosted nirmatrelvir (Paxlovid®) by Pfizer and molnupiravir by Merck, which promise to minimize the incidence of hospitalizations and deaths (National Institute of Health, 2021; Kozlov, 2022).

Molnupiravir, previously known as EIDD-2801, is an isopropyl ester prodrug derived from the ribonucleoside analog β-d-N4-hydroxycytidine (NHC) which is then converted in the cell to its active form, molnupiravir triphosphate (MTP). Similar to other nucleoside analogs such as remdesivir, molnupiravir targets the SARS-CoV-2 RdRp that mediates the replication and translation of the coronavirus genome. The RNA-dependent RNA-polymerase (RdRp) is a key enzyme that plays an important role in replicating SARS-CoV-2, making it a promising drug target in developing antiviral therapy for COVID-19 (Imran et al., 2021; Pourkarim et al., 2022). In contrast to remdesivir and monoclonal antibodies that require intravenous administration in health care settings, molnupiravir is available for oral use

because of its better oral bioavailability (Li et al., 2022; Malone and Campbell, 2021; Pouramini et al., 2022).

Molnupiravir was originally developed as antiviral therapy for influenza. However, this antiviral has also shown activity against various other viruses, including SARS-CoV-2. The drug co-developed by Emory University, Ridgeback Biotherapeutics, and Merck is a promising oral treatment for COVID-19 and is expected to be available in the second half of 2022. Molnupiravir has passed preclinical trials in several animal models (rat, hamster, and ferret) and human respiratory epithelial cell cultures, and it has been proven that oral administration of molnupiravir can inhibit the replication of SARS-CoV-2 with strong and broad-spectrum antiviral activity (Renn et al., 2021; Rosenke et al., 2021; Singla and Goyal, 2022). Completed and published phase 1 and phase 2 clinical trials show a good safety, tolerability, and oral bioavailability profile of molnupiravir and support the use for the treatment of COVID-19 (Imran et al., 2021). Several phases 2 and 3 clinical trials are still ongoing and have not been published yet. This literature review aims to describe the mechanism of action, efficacy, and safety of molnupiravir as a new oral antiviral for the prevention and treatment of COVID-19 based on in vivo and clinical studies.

RESEARCH METHODOLOGY

Relevant articles were explored on electronic databases, including Google Scholar, PubMed, and Science Direct using a combination of the following keywords Molnupiravir or EIDD-2801/MK-4482, COVID-19, SARS-CoV-2. The inclusion criteria were articles that reported the clinical trials and laboratory studies on molnupiravir as an antiviral for COVID-19 published from December 2019 to January 2022. The exclusion criteria included non-relevant research, non-English articles, and no full text. The flowchart of article selection can be seen in Figure 1. Ongoing and completed clinical trials were obtained from the ClinicalTrials.gov databank. All studies obtained were reviewed narratively.

RESULT AND DISCUSSION

Pathophysiology of COVID-19

Coronaviruses are a large family of viruses that can cause infectious diseases in animals and humans. In humans, it is known that several coronaviruses cause respiratory tract infections that can range from the common cold to more severe diseases such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and COVID-19 (Martines et al., 2020). Coronaviruses have a very small size with a diameter of 65-125 nm and contain single-stranded RNA as nucleic material, with lengths ranging from 26 to 32 kilobases, consisting of four subgroups, namely, alpha (α), beta (β), gamma (γ), and delta (δ) (Ouassou et al., 2020). Coronavirus disease 2019 (COVID-19) is caused by a novel beta-coronavirus also known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Bohn et al., 2020). Although the main clinical manifestations of infection with the 2019-nCoV coronavirus (SARS-CoV-2), MERS-CoV, and SARS-CoV are similar, the transmission rate of SARS-CoV-2 is very high and the increased reproductive rate compared to the other species make SARS-CoV-2 has the greater risk to public health (Singh et al., 2021[b]).

Symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days. The most common symptoms are fever, cough, and fatigue, as well as other symptoms such as sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia. COVID-19 exhibits several unique clinical symptoms that target the lower respiratory tract, as evidenced by upper respiratory symptoms such as rhinorrhea, sneezing, and sore throat. Patients infected with SARS-CoV-2 also experience gastrointestinal symptoms such as diarrhea, unlike MERS-CoV and SARS-CoV patients

who only experience diarrhea (Rothan and Byrareddy, 2020).

SARS-CoV-2 is transmitted through droplets and aerosols from person to person. Viruses that enter the body bind to host receptors and enter host cells through endocytosis or membrane fusion (Parasher, 2021). SARS-CoV-2 consists of four main structural glycoproteins, namely spike (S), membrane (M), envelope (E), and nucleocapsid (N) glycoproteins. Spike is the largest and most important protein, stands out along the viral surface, and consists of 2 functional subunits. The S1 subunit is responsible for binding to host cell receptors and the S2 subunit is responsible for the fusion of viral and cellular membranes. Structural and functional analysis showed that the SARS-CoV-2 spike also binds to angiotensin-converting enzyme 2 (ACE2), a functional receptor for SARS-CoV (Yuki et al., 2020).

SARS-CoV-2 enters epithelial cells by endocytosis or membrane fusion by binding to the ACE2 receptor and releasing RNA into the cytoplasm. Transmembrane serine protease type 2 (TMPRSS2) in host cells activates protein S and cleaves ACE2 receptors that mediate coronavirus entry into host cells. Positive-sense RNA viral genomes are released into the cell cytoplasm and undergo translation and replication to form progeny genomes and sub-genomic mRNA, which are then translated into membrane proteins, N proteins, and various other proteins. SARS-CoV has its central enzyme called RNA-dependent RNA-polymerase (RdRp). Together with other viruses and cellular proteins, it composes the main replication complex responsible for replicating the viral genome. Viral structural proteins (S, E, and M) assemble in the rough endoplasmic reticulum (RER). The viral structure and nucleocapsid are further assembled in the endoplasmic reticulum Golgi intermediate (ERGIC). The new virions packaged in Golgi vesicles fuse with the plasma membrane and are released by exocytosis (Chams et al., 2020; Wiersinga et al., 2020).

SARS-CoV-2 infection induces inflammatory factors that activate macrophages and dendritic cells, which are antigen-presenting cells (APCs). The presence of SARS-CoV-2 antigen through major histocompatibility complexes I and II (MHC I and II) stimulates humoral and cellular immunity mediated by B cells and T cells. It results in the production of cytokines and antibodies. In advanced stages of infection, accelerated viral replication disrupts the integrity of the epithelial-endothelial barrier. The virus reaches the lower respiratory tract and infects type II pneumocytes causing apoptosis and surfactant loss. The persistent inflammatory responses cause alveolar interstitial thickening, increased vascular permeability, and edema. Pulmonary edema can fill the alveolar cavities with the formation of hyaline membranes. All these pathological changes result in alveolar damage and collapse, leading to impaired gas exchange (Chams et al., 2020; Wiersinga et al., 2020).

Antiviral Therapy in COVID-19

Antiviral therapies for SARS-CoV-2 are divided into two broad groups based on their target of the action, namely agents that target viral proteins or RNA and agents that target host proteins which are important for viral replication (Salasc et al., 2022). The viral protein or RNA targets include protein S, viral proteases (nonstructural proteins, NSP-3 and NSP-5), and viral RdRp (NSP-12), the leading viral targets. The targets of host proteins include host proteases that can aid viral entry into cells (ACE-2, TMPRSS2, furin, cathepsin-L), heparin sulfate proteoglycans (HSPGs) that can aid viral cell attachment, eukaryotic translational proteins (translation initiation factor 4A (elF4A), translation elongation factor 1a (eEF1A), endoplasmic reticulum chaperon protein (S1R, etc.)), transcription machinery (inosine monophosphate dehydrogenase, dihydroorotate dehydrogenase, etc.), and host nuclear importer of viral protein (IMPα/β1). These antivirals are summarized in Table 1

(Şimşek Yavuz and Komşuoğlu Çelikyurt, 2021).

Sulfated polysaccharides are found in susceptible host cells and most human viruses and thus may play an important role in viral infection. Several polysaccharides found abundantly in natural sources, especially those converted to sulfated varieties, have been shown to have high and sometimes broad-spectrum antiviral activity levels such as heparin, agar, and dextran sulfate. The antiviral activity of this polyanionic agent is thought to be related to two-step mechanisms. First is the mechanism of inhibition of viral adsorption, in which the polymer will adhere to the surface of the infectious virion and prevent the attachment of the host cell. Second, polyanions can increase the production of cellular interferon, a signal transduction system induced by virus-infected cells to tell adjacent cells to generate a predominantly antiviral intracellular environment. The use of carrageenan in nasal sprays or oral drops as a prophylactic and early-stage treatment against the common cold virus and SARS-CoV-2 is considered a very promising aspect that is currently being evaluated in several clinical trials. The current investigation results can help establish the use of polysaccharides as high-value natural antiviral drugs with low side effects (Ray et al., 2022).

Molnupiravir

Molnupiravir, previously known as EIDD-2801 or MK-4482, is an isopropyl ester prodrug of the ribonucleoside analog β-D-N4-hydroxycytidine (EIDD-1931; N-hydroxycytidine; NHC). NHC has been known to have inhibitory activity against the replication of several viruses, including Chikungunya virus, Venezuelan Equine Encephalitis virus (VEEV), Respiratory Syncytial Virus (RSV), HCV, Norovirus, Influenza A and B, EBOV, and human coronaviruses with minimal cytotoxicity and a high genetic barrier to resistance (Hashemian et al., 2022; Vicenti et al., 2021). The chemical structures of molnupiravir, NHC, and its active metabolite can be seen in Figure 2.

a. Mechanism of Action

The antiviral activity of β-D-N4-hydroxycytidine (NHC), an active metabolite of molnupiravir, against SARS-CoV-2 was >100-fold more active than ribavirin or favipiravir with antiviral activity correlated with the level of mutagenesis in virion RNA (Zhou et al., 2021). Biochemical analysis by Kabinger et al. (2021) found a two-step model in the mechanism of molnupiravir-induced coronavirus RNA mutagenesis, i.e., incorporation and mutagenesis (the illustration can be seen in Figure 3).

In the body, molnupiravir is converted into NHC triphosphate (MTP), the active metabolite, which is then used by the RdRp of SARS-CoV-2 as a substrate. In its triphosphate form, molnupiravir is a substrate for mitochondrial RNA polymerase, which can also incorporate MTP as a U (uracil) or C (cytosine) analog. In the presence of nucleoside triphosphate (NTP) and MTP, M nucleotides are incorporated by SARS-CoV-2 RdRp instead of C or U nucleotides into negative-stranded genomes (−gRNA) or subgenomic RNA (−sgRNA) during +gRNA transcription. The obtained M-containing negative-stranded RNA can then be used as a template for producing mutated +gRNA and positive-stranded subgenomic mRNA (+sgmRNA). The presence of M in the -gRNA causes mutations in the positive-stranded RNA product, thereafter does not support the formation of functional viruses, thereby preventing the reproduction of the pathogen. This mechanism is also known as “error catastrophe” (Kabinger et al., 2021; Malone and Campbell, 2021).

NHC has been shown to have strong in vitro and in vivo activity with a broad antiviral spectrum against many pathogenic RNA viruses. However, risks to host cells may exist due to the side effects of long-term genotoxicity. As Zhou et al. (2021) stated, during exposure to a viral population that undergoes mutagenesis in its RNA form,

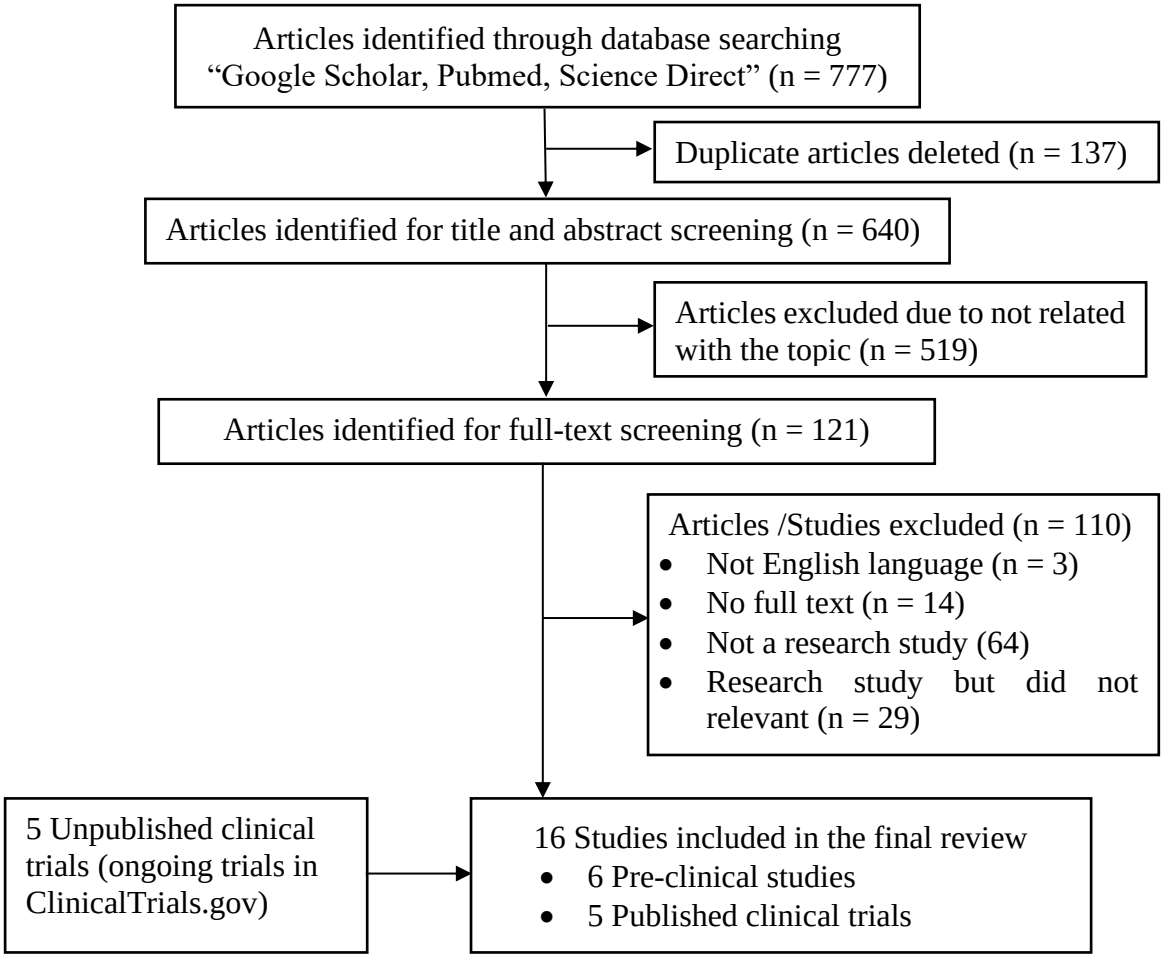
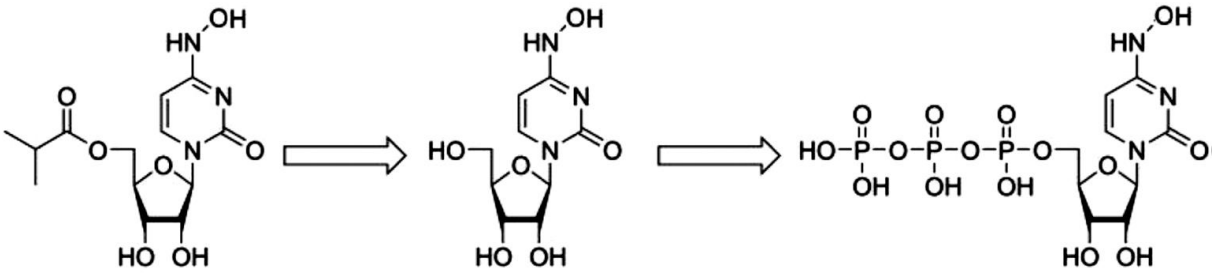


Figure 1. Flowchart of Journal Selection



a **b** **c**

Figure 2. a) EIDD-2801 (Molnupiravir), b) EIDD-1931 (beta-D-N4-hydroxycytidine), c) EIDD-1931-5'-Triphosphate (active metabolite) (Hashemian et al., 2022)

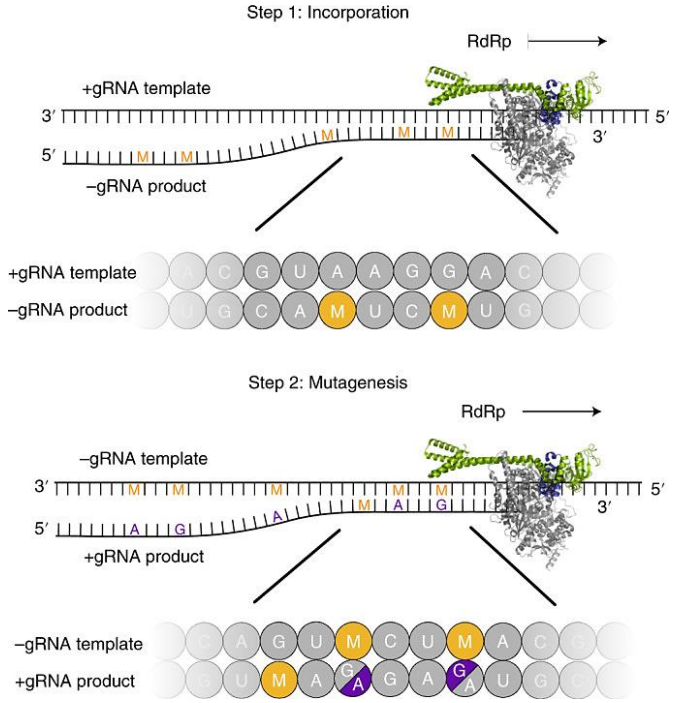


Figure 3. Mechanism of molnupiravir-induced RNA mutagenesis (Kabinger et al., 2021)

Table 1. Group of drugs in clinical and laboratory studies for effective antiviral therapy against SARS-CoV-2 (Şimşek Yavuz and Komşuoğlu Çelikyurt, 2021)

No.	Class	Types
1.	Inhibitors of viral entry into host cell	a) S protein inhibitors: convalescent plasma, monoclonal antibodies, nano bodies, miniproteins, human soluble ACE-2 b) Fusional entry inhibitors : TMPRSS2 inhibitors (camostat, nafamosfat, gabexat, dutasteride, proxalutamide, bromhexin, nitazoxanid, niclosamide) c) Endosomal entry inhibitors: Catepsin L inhibitors (teicoplanin, SSAA09E1, K1777), furin inhibitors (dec-RVKR-cmk), NIP1 inhibitors (EG00229), hydroxychloroquine, nitazoxanide, niclozamide, umifenovir d) HSPG inhibitors : lactoferin
2.	Inhibitors of viral proteases	a) Viral main protease inhibitors (Mpro) : lopinavir/ritonavir, PF-07321332, PF-07304814, GC376 b) Viral papain-like protease inhibitors (PL pro)
3.	Inhibitors of viral RNA	a) RdRp inhibitors : remdesivir, favipiravir, molnupiravir, AT-527 b) Host protein supporting viral RNA synthesis inhibitors : inosine monophosphate dehydrogenase inhibitor (merimepodib), dihydroorarate dehydrogenase inhibitor (PTC299)
4.	Inhibitors of host proteins supporting viral protein synthesis:	a) eEF1a inhibitors : plitidepsin b) S1R agonist : fluvoxamine
5.	Inhibitors of viral immunomodulation	Host importin (IMPα/β1) inhibitors : ivermectin
6.	Agents supporting host natural immunity	Interferon

Table 2. The outline of registered clinical trials about molnupiravir for COVID-19 treatment in ClinicalTrials.gov (accessed on January 16, 2022)

IDs / Status Published or Unpublished	Phase / Study Design / Total Participants	Interventions	Primary Outcome Measures (Results For Published Study)	Side Effects
NCT04575584 / Terminated / Stopped, Unpublished	Phase 2/3 / Randomized, Placebo-Controlled, Double-Blind / 304	I) Molnupiravir 200 mg, 400 mg, 800 mg BID for 5 days vs Placebo II) Molnupiravir (dose to be selected) BID for 5 days vs Placebo	- Recovery time (through day 29) - Percentage of participants with adverse events (through 7 months) and participants who stopped intervention due to adverse events (through day 6) - The study has stopped.	No study results (study has stopped)
NCT04392219 / Completed / Published (Painter et al.)	Phase 1 / Randomized, Placebo-Controlled, Double-Blind / 130	I) Single-dose molnupiravir from 50–1600 mg vs placebo (64 participants with 3:1 ratio) given orally for 5.5 days II) Single dose of molnupiravir 200 mg (10 participants with 1:1 ratio in fed or fasted condition) III) Multiple doses of molnupravir BID 50–800 mg vs placebo (56 participants with 3:1 ratio) given orally for 5.5 days	- Total participants with treatment emergent adverse events and the severity (through 15 days) in single-dose groups (I). - Total participants with treatment emergent adverse events and the severity (through 20 days) in multiple-dose groups (II). - In both single and multiple dose interventions, molnupiravir has been shown to be safe and well-tolerated. - In the food effect evaluation group, the absorption rate of molnupiravir was lower in the fed condition than in the fasting condition but not significantly different.	- The placebo group had a higher incidence of adverse events than the molnupiravir group in both single and multiple dose interventions (43.8% vs 35.4% and 50.0% vs 42.9%, respectively). - In the single-dose intervention, headache was the most common adverse event and was greater in the placebo group than in the molnupiravir group (18.8% vs 12.5%) - In the multiple-dose intervention, diarrhea was the most common adverse event with the same incidence in both placebo and drug groups (7,1%). One subject discontinued the study because of pruritus and rash following molnupiravir 800 mg BID. - In the food effect evaluation group, 3 of 10 participants each reported 1 mild side effect (grade 1)
NCT04405570 / Completed / Published (Fischer et al.)	Phase 2 / Randomized, Placebo-Controlled, Double-Blind / 202	I) Molnupiravir 200 mg BID for 5 days (23 participants) II) Molnupiravir 400 mg BID for 5 days (62 participants) III) Molnupiravir 800 mg BID for 5 days (55 participants) IV) Placebo BID for 5 days (62)	- Time to viral RNA clearance (through day 28) is the primary endpoint. It was significantly decreased in participants with molnupiravir 800 mg compared to the placebo group (14 days vs 15 days, logPvalue=0,013).	- The only adverse events shown by 4 participants were headache, insomnia, and increased alanine aminotransferase (ALT). - Both molnupiravir and placebo groups had minimal adverse events with the lowest found in the molnupiravir 800 mg group.

			- Virologic efficacy (through day 28) and total participants with adverse events grade ≥3(through day 28) - On day 3, infectious virus isolation (secondary endpoint) detected in the molnupiravir 800 mg group was lower than in the placebo group (1,9% vs 16,7%, p=0,016) and on day 5 there was no infectious virus detected in the molnupiravir 400 mg and 800 mg group compared to placebo group as much as 11,1% (p=0,034 & p=0,027, resepectively). - Molnupiravir was well tolerated.	- Two (1,4%) adverse events of molnupiravir led to discontinuation compared to one (1,6%) of placebo group. Grade 3 or higher adverse events was lower in molnupiravir group compared to placebo group (5% vs 8,1%) - Four serious adverse events and led to hospitalization: 1 (1,6%) in the placebo had hypoxia, 2 (3,2%) in the molnupiravir 400 mg had cerebrovascular and oxygen saturation problem and 1 (1,8%) in the molnupiravir 800 mg had acute respiratory failure.
NCT04405739 / Recruiting / Unpublished	Phase 2 / Randomized, Placebo-Controlled, Double-Blind / 96	Molnupiravir vs Placebo BID for 5 days	Total of participants with viral RNA clearance, participants with any adverse events, and participants with serious adverse events through day 28.	No results posted (being evaluated)
NCT04939428 / Recruiting / Unpublished	Phase 3 / Randomized, Placebo-Controlled, Double-Blind / 1332	Molnupiravir 800 mg vs Placebo BID for 5 days	- Percentage of participants with confirmed-COVID-19 (through day 14) - Percentage of participants with at least 1 adverse event (through day 29), and - Percentage of participants with stopped intervention due to the adverse events (through day 5) - Being evaluated. The expected result is that molnupiravir can prevent covid-19 infection (prophylactic properties)	No results posted (being evaluated)
NCT04575597 / Completed / Published (Jayk Bernal et al.)	Phase 3 / Randomized, Placebo-Controlled, Double-Blind /	I) Molnupiravir 200 mg, 400 mg, 800 mg vs Placebo BID for 5 days	- Percentage of incidence of hospitalization and/or deaths (through day 29). The incidence of hospitalization or death was lower in the molnupiravir group than in the	- The adverse events in both groups were similar. Molnupiravir group was lower than placebo group (30,4% or 216 of 710 patients vs 33,0% or 231 of 701 patients)

	1433	II) Molnupiravir 800 mg (dose selected) vs Placebo BID for 5 days	placebo group (6,8% or 48 of 709 patients vs 9,7% or 68 of 699 patients, respectively). The incidence of death was reported 1 vs 9 in molnupiravir group and placebo group. - Percentage of participants with adverse events (through 7 months). - Percentage of participants who stopped intervention due to adverse events (through day 6).	- The most frequently reported (occurred in ≥2% of participants) were COVID-19 pneumonia (6,3% in molnupiravir group vs 9,6% in placebo group), diarrhea (2,3% vs 3,0%), bacterial pneumonia (2,0% vs 1,6%), and worsening of COVID-19 (7,9% vs 9,8%). - The most frequently reported (occurred in ≥1% of participants) were diarrhea (1,7% vs 2,1%), nausea (1,4% vs 0,7%) and dizziness (1,0% vs 0,7%)
NCT04746183 / Recruiting / Unpublished	Phase 2 / Open-label, Randomized / 600	I) Oral molnupiravir BID for 5-6 days vs standard of care as control vs placebo II) Oral nitazoxanide BID for 7 days (initial dose starts with 1500 mg BID) III) Single-dose VIR-7832 by IV infusion (initial dose starts with 50 mg) with 500 mg VIR-7832 IV infusion in 1 hour as active comparator vs Placebo IV infusion over 1 hour.	- Establishment of the optimum dose (phase 1), activity and safety (phase 2), dose-related toxicity (phase 1), and capability of molnupiravir to reduce hospitalization, oxygen saturation, or death (phase 2).	No results posted (being evaluated)

the host cell may be exposed in its DNA form. Even short-term therapy does not prevent the host from this exposure because both of RNA precursors affect the virus and DNA precursors that affect the host through the common intermediate of ribonucleoside diphosphate.

b. Discovery & Development

Molnupiravir (EIDD-2801), which is currently available in oral form, was developed by the Emory Institute of Drug Development (EIDD) and Drug Innovation Ventures (DRIVE) at Emory University (USA) under Ridgeback license with development funding by Wayne & Wendy Holman and Merck (Painter et al., 2021[a]; Rusu et al., 2021). Molnupiravir is packaged in "Swedish Orange" opaque capsules under the co-production of Merck & Ridgeback (Merck, 2021).

Since 2013, EIDD-2801 has been expected to be one of the agents with promising antiviral properties. However, the main focus was orally treating encephalitic New World alphavirus VEEV infection. In early 2020, the development of EIDD-2801 focused on treating influenza. However, due to the emergence of the COVID-19 pandemic, the focus of the development of EIDD-2801, which was later given the generic name molnupiravir, eventually shifted to antiviral strategies in the treatment of COVID-19 (Painter et al., 2021[a]). Molnupiravir is currently under phase 3 clinical trial investigation and has been granted Emergency Use Authorization (EUAs) by the FDA as an oral antiviral drug for non-hospitalized COVID-19 patients in late December 2021.

c. Preclinical Studies

Before the COVID-19 pandemic, molnupiravir (EIDD-2801) had been developed as a new strategy for influenza treatment. Several studies have demonstrated the antiviral activity of EIDD-1931 or NHC (the parent drug of molnupiravir) in experimental animals. The synthesis of molnupiravir from the NHC provides an excellent oral bioavailability profile in ferrets and non-human primate models than the parent drug itself (Toots et al., 2019). Further research then confirms that molnupiravir is a promising anti-influenza clinical candidate with strong and broad-spectrum antiviral activity evaluated in ferrets, mice, and human airway epithelial cell cultures (Sheahan et al., 2020; Toots et al., 2020).

Due to its broad antiviral activity against various RNA viruses, it is suspected that NHC has similar activity against coronaviruses. A study proved that this drug could inhibit the replication of MERS-CoV, SARS-CoV, and SARS-CoV-2 viruses. Administration of EIDD-2801 both as prophylactic and therapeutic in MERS-CoV-infected and SARS-CoV-infected mice showed an increased pulmonary function, bodyweight loss, and decreased viral load that were associated with lethal mutagenesis in RNA viruses. This is similar to the results by Wahl et al. (2021) that evaluated the prophylactic and therapeutic properties of molnupiravir on the inhibition of SARS-CoV-2 replication in mice implanted with human lung tissue (Lung-only Mice, LoM).

In vivo study by Cox et al. (2021) found that giving molnupiravir twice a day significantly reduced the SARS-CoV-2 load in infected ferrets (intentionally inoculated through the upper respiratory tract) and suppressed the transmission of SARS-CoV-2 to healthy ferrets. A study evaluating the efficacy of combination therapy with two antivirals was conducted by Abdelnabi et al. (2021). Combination therapy of favipiravir and molnupiravir (300+150 mg/kg twice daily) 1 hour before intranasal SARS-CoV-2 inoculation for up to 4 days resulted in a significant reduction in viral titers and lung histopathological improvement effect compared to favipiravir or molnupiravir alone in infected hamsters. The administration of this combination therapy showed an increase in the frequency of viral mutations.

d. Clinical Studies

Based on the ClinicalTrials.gov database, seven clinical trials have been conducted evaluating the efficacy of molnupiravir for the treatment of COVID-19. Some of them have been completed and

published while others are still ongoing. The seven clinical trials were summarized in Table 2 (Update as of January 18, 2022). The first-in-human phase 1 clinical trial of molnupiravir (NCT04392219) was conducted by (Painter et al., 2021[b]) that evaluated the safety, tolerability, and pharmacokinetic profile of molnupiravir in 130 healthy human participants aged 19-60 years, located in the United Kingdom. This study also evaluated the effect of food on the pharmacokinetic profile. This clinical trial revealed that molnupiravir was absorbed and tolerated well under both dose interventions. The incidence of side effects in single-dose administration was fewer than in multiple-dose administration in both the placebo and molnupiravir groups. Overall, the most common side effect was a headache, found in both intervention groups with a greater incidence was in single-dose administration (18.8% placebo vs 12.5% molnupiravir). In multiple-dose administration, diarrhea was the most common side effect with the same incidence of molnupiravir and placebo groups (7.1%). One participant developed a rash (mild, grade 1) after twice-daily molnupiravir 800 mg administration and discontinued the study. Meanwhile, in the food evaluation group, three incidents were reported in total in three participants (mild, grade 1). None of the serious side effects was found in all interventions. No increase in the severity of side effects occurred by increasing the dose. Examination of electrocardiogram, vital signs, and clinical laboratory including hematological significantly did not show negatively clinical changes in results.

Another phase 1 clinical trial by Khoo et al. (2021) has been published. The study with ID number NCT04746183 (ClinicalTrials.gov) has progressed to a phase 2 trial and is expected to be completed by April 30, 2022. Similar to the previously mentioned study, this study evaluates the safety, tolerability, and pharmacokinetics of multiple-dose molnupiravir. A total of 18 adult patients with SARS-CoV-2 infection were evaluated through intervention with twice daily molnupiravir vs placebo in a 2:1 ratio with 3 sequential doses of molnupiravir (300 mg, 600 mg, 800 mg). This study established that molnupiravir at a dose of 800 mg twice daily was safe and well-tolerated and had the least incidence of side effects (25% or 1 in 4 patients, experiencing symptoms of anxiety and palpitations). Overall, the side effects reported were mild (grade 1-2) including flu-like symptoms, headache, nausea, diarrhea, and myalgia, found in 9 of 12 patients on molnupiravir and 5 of 6 controls. The pharmacokinetic profiles of these two clinical trials are discussed in the next subsection.

There are three phase-2 clinical trials registered on ClinicalTrials.gov. One of them (NCT04405570) has been completed and published. The other two (NCT04405739 and NCT04746183) that are still ongoing are summarized in Table 2. The phase 2a double-blind, placebo-controlled, randomized, multicenter clinical trial by Fischer et al. (2021) evaluating the antiviral efficacy, safety, and tolerability of molnupiravir as a COVID-19 treatment was conducted in 202 outpatients with confirmed COVID-19 within 96 hours and had symptom onset within 7 days which were observed for 28 days since the treatment initiation. Participants were randomized into groups of molnupiravir 200 mg, 400 mg, 800 mg, and placebo.

Antiviral efficacy and infectious virus isolation were assessed by reverse transcriptase-polymerase chain reaction (RT-PCR) examination of viral RNA inoculated from nasopharyngeal swabs on days 1, 3, 5, 7, 14, and 28. Virologic efficacy was measured by assessing the duration of the first non-detectable SARS-CoV-2 RNA in nasopharyngeal swabs since initiation (day 1) known as a time to viral clearance. Compared to the placebo group, time to viral RNA clearance was significantly shorter in the twice-daily 800 mg molnupiravir group ($p= 0.013$, median 14 days vs 15 days). At the end of the study (day 28), the proportion of participants who achieved viral RNA clearance was greater in the 800 mg molnupiravir group (92.5%) compared to 200 mg molnupiravir, 400 mg molnupiravir, and

placebo groups (91.3%, 78.7%, and 80.3%, respectively). Infectious virus isolation was significantly lower in the 800 mg molnupiravir group compared with the placebo group on day 3 of treatment (1.9% vs. 16.7%, p=0.016). On day 5, there was no isolation from the 400 mg and 800 mg molnupiravir groups compared to placebo (11.1%). On day 28, the proportion of participants treated with molnupiravir who developed antibodies to SARS-CoV-2 was greater than in participants who received a placebo (99.2% vs. 96.5%).

Only a few side effects were found in this study. The molnupiravir and placebo groups had minimal adverse events with the lowest incidence found in the 800 mg molnupiravir group. Headache, insomnia, and elevated ALT values were side effects reported by more than four patients and there were no significant differences in the intervention group or dose level. Adverse events with grade ≥3 were found in all molnupiravir and placebo groups of 5.0% and 8.1%, respectively. There were no dose-related tendencies found in the results of clinical chemistry and hematology examinations. This phase-2 trial revealed that twice-daily molnupiravir 800 mg orally was safe and well-tolerated, with accelerated clearance of SARS-CoV-2 and elimination of the infectious virus (Fischer et al., 2021).

There are two ongoing phase-3 clinical trials under the ClinicalTrials.gov registry (NCT04939428 and NCT04575597). One of them (NCT04575597) has published the final results and discontinued earlier before the estimated completion date because this study has shown satisfying results with greater benefit in the molnupiravir treatment group than in the placebo (Singh et al., 2021[a]). The phase 3, double-blind, placebo-controlled, randomized clinical trial (MOVe-OUT, NCT04575597) by Jayk Bernal et al. (2021) compared the use of molnupiravir 800 mg with placebo. Molnupiravir and placebo were randomly administered orally every 12 hours for 5 days to 1433 participants (from the initial target of 1850 participants) who were non-hospitalized unvaccinated adult patients with symptom onset within five days and at high risk of developing severe COVID-19 symptoms. The interim analysis results in 54.1% of the target population showed that the risk of hospitalization or death through day 29 was lower in the molnupiravir group (7.3% or 28 of 385 participants) than in the placebo group (14.1% or 53 of 377 participants). The final analysis showed consistent results. The molnupiravir group was shown to have a lower risk of hospitalization or death through day 29 (6.8% or 48 of 709 participants) than the placebo group (9.7% or 86 of 699 participants). One death in the molnupiravir group and nine deaths in the placebo group were reported through day 29. Meanwhile, the incidence of side effects in the two groups did not show significantly different results (30.4% and 33.0% for molnupiravir and placebo groups, respectively. The most common side effects reported in ≥2% of participants were COVID-19 pneumonia (6.3% in the molnupiravir group vs. 9.6% in the placebo group), diarrhea (2.3% vs. 3.0%), and bacterial pneumonia (2.0% vs 1.6%), and worsening of COVID-19 due to side effects (7.9% vs 9.8%). Diarrhea, nausea and dizziness were the most common side effects found in ≥1% of participants (1.7% vs 2.1%, 1.4% vs 0.7%, 1.0% vs 0.7% in the molnupiravir vs placebo groups, respectively).

Another ongoing phase 3 clinical trial (NCT04939428, MOVe-AHEAD) aims to determine the efficacy of molnupiravir in preventing COVID-19 in healthy adult patients in contact with COVID-19 patients through day 14. Meanwhile, one phase 3 clinical trial (NCT04575584, MOVe-IN) has been discontinued due to no clinical benefit shown in the interim results (CinicalTrials.gov).

e. Pharmacokinetic Profiles

Based on a dose-escalation phase 1 clinical trial (NCT0476183) to characterize the pharmacokinetics of the prodrug molnupiravir and its metabolite form EIDD-931, it was found that the prodrug molnupiravir was generally unquantifiable. It was detected at low concentrations only at

initial time points (0.5 and 1 hour after dosing) at all doses (300 mg, 600 mg, and 800 mg). Plasma sampling was performed on day 1 and day 5. Plasma concentrations of EIDD-1931 (NHC) were detected without accumulation on days 1 - 5. The geometric mean (% Coefficient of Variation) of NHC at 4 hours after dosing for each dose level were 3470 (42.4), 3880 (56.3), and (7880) 39.0 ng.h/ml on day 5. Maximum concentrations (C_{max}) at each dose of 300 mg, 600 mg and 800 mg were 1620 (51.0), 1820 (84.6) and 4180 (28.1) ng/ml with time to maximum concentration (T_{max}) ranged from 0.5 to 2.0 hours (Khoo et al., 2021).

Similar to the clinical trial above, the concentrations of molnupiravir were generally below the limit of quantification at doses up to 800 mg in single ascending dose administration and up to 400 mg in multiple ascending dose administration in the NCT04392219 trial. Both in single and multiple doses, the pharmacokinetic parameters of molnupiravir were not calculated at doses up to 400 mg. In the single ascending dose group, the mean maximum concentration (C_{max}) is up to 13.2 ng/ml with a median time to maximum concentration (T_{max}) of 0.2-0.75 hours on a single dose of molnupiravir between doses of 600-1600 mg. The amount of molnupiravir was detectable in urine, representing 0.002% of the dose of 800 mg. EIDD-1931 was rapidly detected in plasma upon oral molnupiravir up to 800 mg with a median T_{max} of 1 hour and a geometrical mean elimination half-life ($t_{1/2}$) between 0.907-1.29 hours. Meanwhile, the values of T_{max} for the remaining doses (1200 mg and 1600 mg) were postponed at 1.75 hours and 1.5 hours, with the elimination half-life also being longer to 1.81 and 4.59 hours, respectively. Urinary excretion of EIDD-1931 (within 24 hours post-dose) consistently increased with the increasing dose, generally excreted within the first 4 hours post-dose. The percentages of the dose excreted in urine (apparent clearance or CL_R) at the smallest dose of 50 mg and the largest dose of 1600 mg were 0.820% and 6.70%, respectively (Painter et al., 2021[b]).

In twice-daily multiple ascending doses, molnupiravir concentrations were measurable in all but 1 participant at 0.5 hours post-dose with an 800 mg dose level on day one and day 5. Post oral administration, EIDD-1931 was rapidly seen in plasma following oral molnupiravir on all doses (50–800 mg) with median T_{max} between 1.0 and 1.75 hours on day one and day 6. On day one and day 6, respectively, plasma concentrations decreased essentially monophasically at all dose levels (t1/2 ranged from 0.918 to 1.18 h) and at 200 mg and most subjects at 300 mg and 400 mg doses. At a dose of 600 mg, the lack of a clear terminal elimination phase confounds the evaluation of $t_{1/2}$ for most subjects. At a dose of 800 mg, the mean $t_{1/2}$ was 7.08 hours. There was no dose accumulation with the accumulation ratio of the area under the plasma concentration-time curve during a dosing interval (RA_{AUCt}) between 0.938-1.16 dan the accumulation ratio of maximum concentration (RA_{Cmax}) in between 0.843-1.10 in all dose cohorts. Similar to single ascending doses, EIDD-1931 was mostly excreted in the urine within the first 4 hours post-dose on both days, with a dose percentage excreted between 0.854% and 3.61% (Painter et al., 2021[b]).

Similar to the single- and multiple-ascending dose interventions, evaluation of food effect on the absorption rate of molnupiravir administered at a dose of 200 mg orally in the fasted and fed conditions (1:1 ratio of 20 participants) showed that molnupiravir concentrations were generally below the limit of quantification and the pharmacokinetic parameters were not measurable. EIDD-1931 concentrations were measurable in the fasting state at 0.25 h postdose (two subjects) and in the fed state at 0.5–1.5 h postdose. Administration of molnupiravir 200 mg in the fed condition slowed the rate of drug absorption, with the reported mean Cmax value being significantly decreased by 35.6% compared to the fasted condition (893 ng/ml vs 575 ng/ml in the fasted and fed conditions, respectively) as well as the median Tmax value which delayed to 3 hours postdose compared to 1 hour

postdose in fasted condition. However, the mean t1/2 in fasted and fed conditions were similar, about 1 hour (0.977 hours and 1.09 hours, respectively). In the presence of food intake, urine pharmacokinetics did not show significantly different parameters (CL_R value of 1,04% and 1,12% in fed and fasted condition, respectively) (Painter et al., 2021[b]).

Only a few amounts of molnupiravir or EIDD-1931 were detected in the urine, which is thought to be related to the metabolism of EIDD-1931 to cytidine and uridine. Molnupiravir 800 mg demonstrated a good bioavailability dan tolerability after oral administration to healthy volunteers and SARS-CoV-2-infected patients. However, further large-scale research is still needed (Painter et al., 2021[b]).

CONCLUSIONS

Molnupiravir is a promising breakthrough for high-risk COVID-19 patients to reduce the risk of hospitalization and/or death by up to 50%. Molnupiravir exhibits dose-dependent pharmacokinetics with effective doses for SARS-CoV-2 at doses of 200 mg to 800 mg. The absorption rate in the fed or fasted conditions is similar so that patient can take it with or without food. Molnupiravir is safe and well-tolerated at doses of 800 mg twice daily with minimal side effects, generally of mild to moderate grade such as headache, nausea and diarrhea. Paxlovid is also available for oral administration but its use is limited due to potential drug interactions and is not recommended for patients with severe renal or hepatic impairment. Remdesivir and sotrovimab, which also EUA approved COVID-19 therapies, are of limited use because they are only available for injection. There are no trial data comparing the clinical efficacy of molnupiravir with other anti-COVID-19 but the FDA recommends its use only when the other options are not available or cannot be given, considering the lack of current research data regarding molnupiravir efficacy so that further large-scale trials are needed to evaluate its effectiveness against COVID-19, pharmacological aspects such as drug interactions, contraindications, toxicity, and its use in specific populations that require dose adjustment.

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