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MINI REVIEW

Molnupiravir: Mechanism of action, clinical, and translational science

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Abstract

Molnupiravir is an oral prodrug of the broadly active, antiviral ribonucleoside analog *N*-hydroxycytidine (NHC). The primary circulating metabolite NHC is taken up into cells and phosphorylated to NHC-triphosphate (NHC-TP). NHC-TP serves as a competitive substrate for viral RNA-dependent RNA polymerase (RdRp), which results in an accumulation of errors in the viral genome, rendering virus replication incompetent. Molnupiravir has demonstrated activity against SARS-CoV-2 both clinically and preclinically and has a high barrier to development of viral resistance. Little to no molnupiravir is observed in plasma due to rapid hydrolysis to NHC. Maximum concentrations of NHC are reached at 1.5 h following administration in a fasted state. The effective half-life of NHC is 3.3 h, reflecting minimal accumulation in the plasma following twice-daily (Q12H) dosing. The terminal half-life of NHC is 20.6 h. NHC-TP exhibits a flatter profile with a lower peak-to-trough ratio compared with NHC, which supports Q12H dosing. Renal and hepatic pathways are not major routes of elimination, as NHC is primarily cleared by metabolism to uridine and cytidine, which then mix with the endogenous nucleotide pools. In a phase III study of nonhospitalized patients with COVID-19 (MOVe-OUT), 5 days of treatment with 800 mg molnupiravir Q12H significantly reduced the incidence of hospitalization or death compared with placebo. Patients treated with molnupiravir also had a greater reduction in SARS-CoV-2 viral load and improved clinical outcomes, compared with those receiving placebo. The clinical effectiveness of molnupiravir has been further demonstrated in several real-world evidence studies. Molnupiravir is currently authorized or approved in more than 25 countries.

INTRODUCTION

Molnupiravir (formerly EIDD-2801) is a prodrug of the ribonucleoside analog *N*-hydroxycytidine (NHC) (β-D-N4-hydroxycytidine [formerly EIDD-1931]) with antiviral activity against SARS-CoV-2 variants.[1] NHC acts as a competitive substrate for virally encoded RNA-dependent RNA polymerase (RdRp) and introduces errors into the viral genome, a mechanism known as viral error induction.[1,2]

Oral molnupiravir is rapidly hydrolyzed to NHC, the primary circulating metabolite. Circulating NHC is then taken up into cells where it is phosphorylated to its triphosphate anabolite NHC-TP (formerly EIDD-2061; Figure 1).[3] It is primarily cleared from the body via metabolism to endogenous pyrimidines (cytidine and uridine) which mix with the endogenous nucleoside pools. Renal excretion of NHC is not a major elimination pathway because of more rapid intracellular metabolism. In vitro, molnupiravir and NHC are not substrates, inducers, or inhibitors of major xenobiotic drug-metabolizing enzymes and transporters (other than substrates of nucleoside uptake transporters).

Molnupiravir was evaluated in a global phase II/III study of nonhospitalized adults with mild-to-moderate coronavirus disease 2019 (COVID-19; MOVe-OUT).[4] Compared with placebo, treatment with molnupiravir significantly reduced the percentage of participants who were hospitalized or died through day 29 (6.8% vs. 9.7%; difference −3.0 percentage points; 95% confidence interval −5.9 to −0.1). Molnupiravir was also associated with fewer deaths compared with placebo, and treatment was well tolerated. The antiviral activity and further evidence of the clinical benefit of molnupiravir have also been demonstrated in other randomized controlled trials and real-world evidence studies. This review aims to summarize the regulatory status, mechanism of action, clinical pharmacology profile, and key clinical studies for molnupiravir.

Clinical & Translational Card for Molnupiravir

Mechanism of Action: viral error induction

Indication (s): treatment of mild-to-moderate COVID-19

Dosage and Administration: 800 mg administered orally every 12 h for 5 days

Major Metabolic Pathway: hydrolysis, phosphorylation

Key PK Characteristics: plasma NHC AUC of 8810 h*ng/mL, C_{max} of 2600 ng/mL, Tmax of 1.5 h, effective $t_{1/2}$ of 3.3 h

REGULATORY APPROVAL

The World Health Organization (WHO) declared the emergence of the novel coronavirus (2019-nCoV) a public health emergency of international concern on January 30, 2020. In response to the pandemic and the urgent unmet medical need for treatment options, the molnupiravir application was submitted to regulatory agencies through special approval pathways (as applicable) available for public health emergency situations.

The first global authorization of molnupiravir was in November 2021 when the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK granted conditional marketing authorization for molnupiravir for the treatment of mild-to-moderate COVID-19 in adults with a positive SARS-COV-2 diagnostic test who also have at least one risk factor for developing severe illness (see later section on MOVe-OUT study design for a full list of risk factors). The US Food and Drug Administration (FDA) granted emergency use authorization on December 23, 2021, for use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults with positive SARS-CoV-2 viral testing who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate. On December 24, 2021, Japan's Ministry of Health, Labor and Welfare granted special approval for emergency in Japan for molnupiravir for the treatment of disease caused by SARS-CoV-2 infection (COVID-19), under Article 14-3 of the Pharmaceuticals and Medical Devices Act to approve a medical product swiftly in an emergency situation to protect public health.

As of July 2023, molnupiravir is approved or authorized for use in more than 25 countries, including the UK, the US, Japan, Australia, and China, for the treatment of certain adults who have been diagnosed with COVID-19. The exact wording of the indication/authorization may vary by country.

MECHANISM OF ACTION

Molnupiravir is the 5′-isobutyrate prodrug of the broadly active, antiviral ribonucleoside analog NHC. Once distributed inside cells, NHC is phosphorylated to NHC-TP, which acts as a competitive alternative substrate for virally encoded RdRp. Molnupiravir is then incorporated (as NHC monophosphate) into the elongating RNA strand. Due to its ability to tautomerize, it can substitute

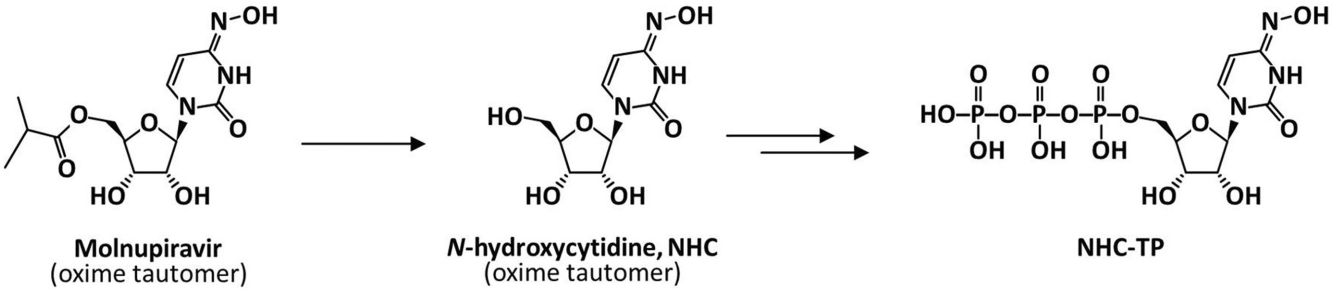

FIGURE 1 Metabolism of molnupiravir to NHC-TP. NHC-TP, *N*-hydroxycytidine triphosphate or EIDD-2061.

for either cytidine or uridine and subsequently pair with either guanosine or adenosine in the RNA template.[5] Molnupiravir does not initiate chain termination, which enables further RNA elongation and production of molnupiravir-containing RNA templates. RdRp then uses molnupiravir-containing RNA templates for replication, which results in an accumulation of nucleotide errors across the viral genome (a mechanism known as viral error induction). Increases in mutation frequencies above a tolerable threshold (i.e., a mutation rate that surpasses the level needed to maintain viral viability) result in production of replication incompetent genomes in subsequent rounds of RNA synthesis, which ultimately leads to noninfectious virus (Figure 2).

This mechanism of action has been validated in vitro for multiple viruses, including SARS-CoV-2. When virus is grown in the presence of NHC, viral genomes have significantly increased levels of nucleotide errors resulting in multi-log decreases in infectious virus. NHC has demonstrated sub- to low-micromolar half maximal effective concentration (EC_{50}) values against SARS-CoV-2, SARS-CoV-1, and MERS-CoV viral replication in multiple cell types.[3,6] As opposed to therapeutic antibodies for COVID-19 treatment which target the viral spike protein, the activity of molnupiravir is not impacted by spike mutations commonly associated with emerging SARS-CoV-2 variants. In vitro studies have shown that molnupiravir has consistent antiviral activity against all SARS-CoV-2 variants (including alpha, beta, gamma, delta, lambda, mu, and omicron). The half-maximal inhibitory concentration (IC50) values for SARS-CoV-2 variants ranged from 0.28 to 5.5 μM and were generally within twofold of the IC50 estimate for the original strain of SARS-CoV-2.[7]

While it has been argued that molnupiravir's unique mechanism of action may lead to new variants, viral error induction introduces amino acid substitutions at random, many of which are likely deleterious to viral replication and confer a high barrier to the development of resistance.[7] In the phase III clinical study, patients had nasal swabs collected to test for SARS-CoV-2 (via both polymerase chain reaction [PCR] and plaque assays) through day 29. Among patients with culturable infectious virus detected at baseline, no culturable infectious virus was detected in any molnupiravir-treated patients by day 3, indicating a low probability of transmitting error-induced SARS-CoV-2 virus.[8] As a consequence, the generation of drug-resistant escape variants by molnupiravir is considered unlikely.

PHARMACOKINETIC/ PHARMACODYNAMIC CHARACTERISTICS

As of July 2023, the pharmacokinetics and pharmacodynamics of molnupiravir have been evaluated in 10 completed clinical trials, including four phase I studies, one phase I/II study, two phase IIa studies, one phase II study, one phase II/III study, and one phase III study (Table 1). Additional studies remain ongoing.

Pharmacokinetics

Following oral administration of the prodrug molnupiravir capsule to healthy volunteers in the fasted state, NHC reaches peak concentrations at approximately 1.5 h following dose administration and then declines in a biphasic manner (Figure 3).[9] Very little molnupiravir prodrug is detected in plasma. Circulating NHC exposures increased in a manner that is approximately proportional to dose, with single-dose exposures being predictive of multiple-dose exposures, indicating lack of saturable uptake and conversion of molnupiravir to NHC at the therapeutic dose range. The effective half-life ($t_{1/2}$) of NHC was determined to be 3.3 h, reflecting minimal accumulation in the plasma following Q12H dosing. The terminal half-life of NHC was estimated to be 20.6 h.[10] The concentration of NHC-TP was evaluated in peripheral blood mononuclear cells (PBMCs) as a surrogate for NHC-TP concentrations at the site of action. The $t_{1/2}$ of NHC-TP in PBMCs was consistent with the terminal $t_{1/2}$ of NHC in plasma and approximately twofold accumulation in NHC-TP

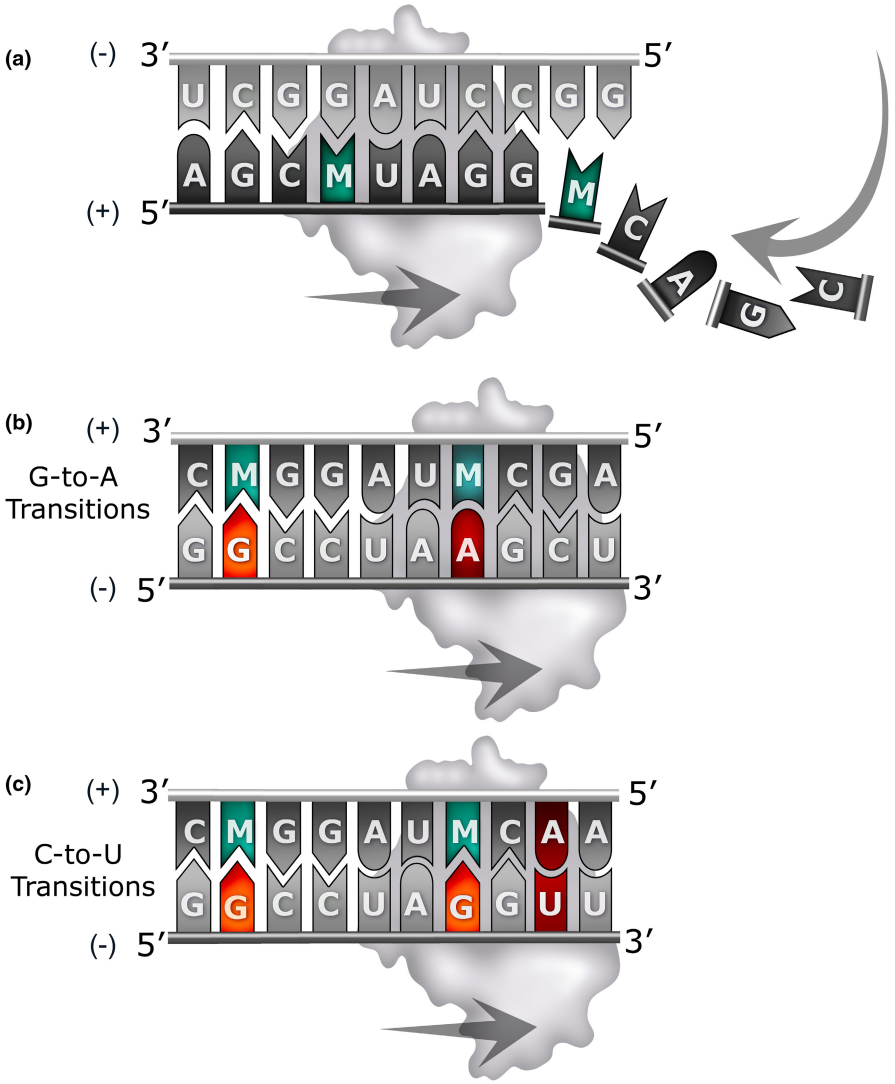

FIGURE 2 Molnupiravir works by a novel mechanism known as viral error induction. The light gray nucleotides make up the negative-sense RNA strand while the dark gray nucleotides make up the positive-sense RNA strand. (a) The active form of molnupiravir (NHC triphosphate, shown as M) competes with other endogenous nucleotides for incorporation (as NHC monophosphate) into the elongating RNA strand by viral RNA-dependent RNA polymerase. (b) G-to-A transitions occur when molnupiravir (in the oxime form) pairs with adenosine (red), but not when molnupiravir (in the hydroxylamine form) pairs with guanine (orange). (c) C-to-U transitions occur when an adenosine-to-uridine pairing replaces a guanosine-to-cytidine pairing in the original template (red). NHC, *N*-hydroxycytidine or EIDD-1931.

area under the concentration–time curve (AUC) was observed with Q12H dosing. The flatter profile and longer $t_{1/2}$ of the more relevant NHC-TP in PBMCs results in high intracellular concentrations of the active moiety being maintained across the dosing interval with a low peak-to-trough ratio, supporting a Q12H dosing regimen for molnupiravir. The AUC of NHC in plasma was highly correlated with NHC-TP exposures in PBMCs, and exposure–response analysis demonstrated that NHC AUC was a stronger predictor of clinical outcomes than NHC trough concentrations.[11]

High capacity and widely distributed CES1 and CES2 carboxylesterases appear responsible for rapid and complete conversion of oral molnupiravir to NHC,[12] primarily during absorption and/or hepatic first pass. Circulating NHC is then taken up into cells via multiple nucleoside uptake transporters (equilibrative nucleoside transporters [ENTs] and concentrative nucleoside transporters [CNTs]) where it is anabolized to NHC-TP via endogenous kinases.[13] The main route of elimination of NHC appears to be metabolism to uridine and cytidine which then mix with the endogenous nucleotide pools.[14] Multiple host cell enzymes have demonstrated this activity, including cytidine deaminase[12] and the mitochondrial amidoxime-reducing components mARC1 and mARC2.[15] As a result, renal excretion is not a major route of elimination of NHC, with only 3% of an 800 mg molnupiravir dose excreted in urine as NHC from 0 to 12 h after administration.[9] Hepatic elimination is also not expected to be a major route of elimination for NHC based on nonclinical data (data not shown). Based on a broad and comprehensive in vitro assessment, both molnupiravir and NHC are not substrates, inhibitors, or inducers of any major xenobiotic enzymes or transporters (excluding nucleoside enzymes or transporters), and as a result have a low potential to initiate or be subject to drug–drug interactions.

Population pharmacokinetics (PK) analysis of NHC concentration has been conducted using data from early- and late-stage studies, including data from the phase III MOVe-OUT study in nonhospitalized adults with

TABLE 1 Summary of completed clinical trials for molnupiravir.

Study category	Study no.	Short title	Phase	*N*	Clinical trial registration
Healthy adult	P004	First-in-human SD and MD	I	130	NCT04392219
	P012	Extended duration MD	I	32	EudraCT 2021-000860-30
Bioavailability	P010	Granules relative bioavailability	I	16	EudraCT 2021-001563-24
Intrinsic factors	P008	SD and MD Japanese	I	65	N/A
Dose ranging	P005	Treatment in nonhospitalized adults (AGILE)	I/II	198	NCT04746183
	P006	Treatment in nonhospitalized adults	IIa	202	NCT04405570
	P007	Treatment in hospitalized adults	IIa	71	NCT04405739
Pivotal	P001	Treatment in hospitalized adults (MOVe-IN)	II/III	293	NCT04575584
	P002	Treatment in nonhospitalized adults (MOVe-OUT)	II/III	1710	NCT04575597
	P013	Prophylaxis (MOVe-AHEAD)	III	1528	NCT04939428

Abbreviations: N, sample size; MD, multiple dose; N/A, not available; SD, single dose.

COVID-19.[16] The PK of NHC was found to be similar between healthy participants and participants with COVID-19. Population PK analysis showed that intrinsic and extrinsic factors do not impact the exposures of NHC to a meaningful extent, as the geometric mean ratio of NHC exposures fell within the clinical bounds (0.7- to 2.0-fold the exposure of the overall population) determined by exposure–response modeling for all populations.[16] Therefore, no dose adjustment is required based on factors such as age, sex, body weight, race, or ethnicity. Further, patients with renal impairment and patients with hepatic impairment do not require dose adjustment, and no dose adjustment is recommended for molnupiravir when co-administered with other medications. Administration of molnupiravir with a high-fat meal delayed the Tmax by 2 h and reduced the C_{max} by 36% but did not impact the AUC of NHC.[9] Since the rate of NHC absorption was slowed, but the extent was not impacted, molnupiravir can be given without regard to food.

Pharmacodynamics and exposure–response

SARS-CoV-2 RNA collected from nasal swabs in two clinical studies was sequenced to characterize the rate of viral errors present in the genome (a measure of the mechanism of action) following treatment with molnupiravir. Overall, a higher rate of errors was observed in the 800 mg dose group, compared with groups to whom lower doses or placebo were administered.[8,17]

Exposure–response (E–R) data confirm the choice of the 800 mg dose for the treatment of mild or moderate COVID-19 with molnupiravir. E–R analysis for the primary efficacy endpoint of hospitalization or death rates through day 29 conducted using the phase III data from MOVe-OUT identified an additive AUC-based maximum effect (E_{max}) model as best representing the exposure dependency in drug effect. The AUC_{50} was estimated to be 19,900 nM hour.[11] Figure S1 demonstrates that NHC exposures produced by an 800 mg dose are near the plateau of the E–R relationship.

E–R relationships for SARS-CoV-2 viral load change from baseline at days 5 and 10, slope of viral load decline, and error rate (a direct measure of mechanism of action) were all highly significant ($p \leq 0.005$) for both evidence of drug effect and exposure dependency.[18] E–R results support a consistent interpretation of dose and exposure dependency for molnupiravir across clinical outcome and pharmacodynamic markers, with exposures at 800 mg falling near the top of the E–R curves. The exposure distributions of the 200 or 400 mg doses fall on the exposure-dependent portions of the E–R curves and, therefore, can be expected to be associated with reduced drug effects relative to 800 mg, supporting the choice of 800 mg over lower doses.[18] The available results suggest that additional clinical benefit from increased doses above 800 mg would at best be modest in magnitude and, overall, the results support the appropriateness of the 800 mg dose choice for molnupiravir.

KEY CLINICAL TRIALS

MOVe-OUT phase II

Molnupiravir was evaluated in MOVe-OUT (NCT04575597), an adaptive phase II/III trial of

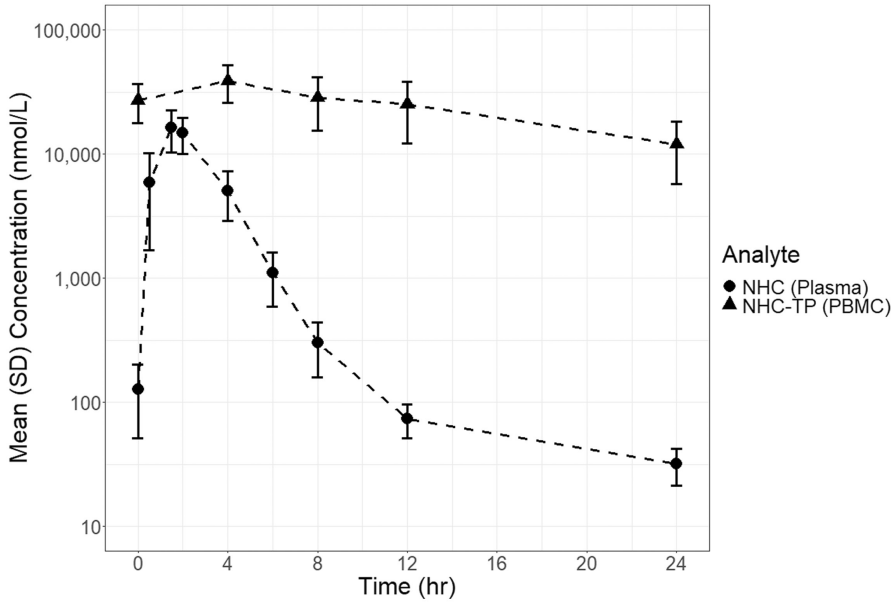

FIGURE 3 Mean (SD) steady-state plasma NHC and PBMC NHC-TP concentration–time profiles in healthy adults ($N=12$) following oral administration of molnupiravir 800 mg Q12H for 10 days.[10] The LLOQ was 4 nmol/L for NHC and 10 nmol/L for NHC-TP. NHC-TP samples for two participants were below the LLOQ at 24 h and were imputed as zero for plotting. LLOQ, lower limit of quantification; NHC, *N*-hydroxycytidine or EIDD-1931; NHC-TP, *N*-hydroxycytidine triphosphate or EIDD-2061; PBMC, peripheral blood mononuclear cell; Q12H, every 12 h; SD, standard deviation.

nonhospitalized adults with COVID-19. The phase II dose-ranging portion was designed to enroll participants with laboratory-confirmed SARS-CoV-2 infection and symptom onset within 7 days before randomization.[19] Participants in phase II were randomized 1:1:1:1 to receive molnupiravir 200, 400, or 800 mg or placebo Q12H for 5 days. The primary efficacy objective was to evaluate the efficacy of molnupiravir compared with placebo, as assessed by the percentage of participants who were hospitalized and/or died through day 29. A total of 302 participants were enrolled in phase II and completed the day 29 visit. The prespecified end of phase II interim analysis showed that all molnupiravir doses were generally well tolerated, with no dose-limiting toxicity observed at the highest dose (800 mg). Because of the small sample size, there was no significant difference in the percentage of participants who were hospitalized or died through day 29 across intervention groups. Post hoc subgroup analyses showed a potential clinical benefit of molnupiravir for participants with time to symptom onset within 5 days of randomization and with risk factors for developing severe COVID-19.[19] The 800 mg dose was selected to advance to phase III.

MOVe-OUT phase III

In the phase III portion of MOVe-OUT, enrolled participants had mild or moderate COVID-19 and at least one risk factor for progression to severe disease. Risk factors included age >60 years, obesity (body mass index ≥30 kg/m^2), chronic kidney disease, chronic obstructive pulmonary disease, serious heart conditions (i.e., heart failure, coronary artery disease, or cardiomyopathies), diabetes mellitus, or active cancer. Participants were randomized 1:1 to receive either molnupiravir 800 mg or placebo Q12H for 5 days within 5 days of symptom onset. At the prespecified interim analysis, 7.3% (28/385) of participants who were treated with molnupiravir were hospitalized or died through day 29 compared with 14.1% (53/377) of participants who received placebo ($p=0.001$).[4] A significant reduction in the primary endpoint was also observed in the analysis of all 1433 randomized participants, where 6.8% (48/709) of participants receiving molnupiravir (48/709) were hospitalized or died through day 29, compared with 9.7% (68/699) receiving placebo. One participant treated with molnupiravir died, compared with nine who were treated with placebo.

Molnupiravir was associated with a greater reduction in SARS-CoV-2 RNA titer compared with the placebo group, as measured by the change from baseline in nasopharyngeal samples at days 3, 5, and 10. Among participants with infectious virus detected at baseline, no molnupiravir-treated participants had infectious virus detected on day 3 or later, whereas 20.8% (20/96) and 2.2% (2/89) of participants in the placebo arm had infectious virus detected on day 3 and day 5, respectively.[8] Overall, the virologic response to molnupiravir observed in MOVe-OUT was consistent, irrespective of baseline viral load,

presence of baseline SARS-CoV-2 antibodies baseline (indicating a humoral immune response against the virus), or SARS-CoV-2 clade.[8]

Treatment with molnupiravir also resulted in improved clinical outcomes for most participant-reported COVID-19 symptoms compared with placebo.[20] Other important clinically relevant benefits were also observed in MOVe-OUT, including faster normalization of C-reactive protein and blood oxygen saturation (SpO_2), decreased need for respiratory interventions, fewer medically attended visits, and among those participants who were hospitalized during the study, treatment with molnupiravir resulted in a shorter hospital stay compared with placebo.[21] The incidence of adverse events was similar between the treatment and placebo groups.

Other clinical studies

Molnupiravir was also evaluated in a phase IIa study of nonhospitalized patients with COVID-19.[22] Patients presenting with a symptom duration of 7 days or less were randomly assigned to receive molnupiravir 200, 400, or 800 mg, or placebo Q12H for 5 days. Time to undetectable SARS-CoV-2 RNA was shorter for the 800 mg treatment group (14 days) compared with the placebo group (15 days). The proportion of participants who achieved undetectable SARS-CoV-2 RNA by the end of the study was greater for participants who received molnupiravir 800 mg, compared with lower dose levels and placebo. Further, only 1.9% (1/53) of molnupiravir-treated participants had detectable infectious virus on day 3, compared with 16.7% (9/54) of placebo-treated participants.[22]

PANORAMIC was a randomized, controlled, prospective, open-label trial conducted in the UK to evaluate the safety and effectiveness of molnupiravir.[23] Participants with COVID-19 over 50 years of age or over 18 years of age with risk factors were randomized 1:1 to receive either molnupiravir 800 mg Q12H for 5 days and standard of care or just standard of care. This trial was conducted during a period when the Omicron variant predominated, and 99% of participants received at least one dose of a COVID-19 vaccine. The overall incidence of hospitalization or death through day 29 was low: 1% (105/12,529) of participants receiving molnupiravir and standard of care, compared with 1% (98/12,525) of participants receiving standard of care alone.[23] The median time to recovery was 6 days shorter in those receiving molnupiravir plus standard of care (9 days; range 5 to 23 days), compared with those receiving just standard of care (15 days, range 7 days to not reached). There were no reported serious adverse events that were definitely related to the study medication.

Several additional real-world evidence studies have demonstrated the effectiveness of molnupiravir, including a study in nonhospitalized patients in Hong Kong, which showed that molnupiravir led to a reduction in death and in-hospital disease progression,[24] and a study of Clalit Health Services in Israel, which showed that treatment with molnupiravir was associated with a reduced risk of severe COVID-19 or COVID-19-related death in older adult patients.[25]

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CONFLICT OF INTEREST STATEMENT

All authors are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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