Safety monitoring of molnupiravir for treatment of mild to moderate COVID-19 infection in low and middle-income countries using cohort event monitoring: a WHO study

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World Health Organization

Use of this protocol

This is a master protocol, which was approved by the WHO Ethics Review Committee (ERC) on 09.03.2022 (protocol ID; CERC.0155. It will be used by study sites who will submit a protocol to their national ERC. The only country-specific changes that should be made will be those to facilitate translation into the local language, address the specific concerns of the local ERC, and to add the names of the national principal investigators (PIs), members of the local study teams and the identity of the study sites. Amended site-specific protocols developed for implementation in countries based on this WHO master protocol must be approved by the WHO ERC prior to implementation.

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WHO will sponsor at least six countries to implement this protocol. If Member States that are not sponsored by WHO wish to adapt and implement the master protocol, sources of funding need to be identified for the site-specific protocols.

Abbreviations

AE	Adverse event
CEM	Cohort event monitoring
COVID-19	Coronavirus disease 2019
ERC	Ethics review committee
GEP	Good epidemiological practice
ICF	Informed consent form
LMIC	Low-to-middle income country
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred term
PV	Pharmacovigilance
PVG	Pharmacovigilance team (WHO Headquarters)
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAE	Serious adverse event
WHO	World Health Organization

Synopsis

Background and rationale: Molnupiravir, has been newly introduced onto the market as the first oral medicine for the treatment of non-severe COVID-19 disease. Pharmacovigilance has an important role to provide further evidence on the safety of this medicine in the general population. Pharmacovigilance will ensure potential safety issues are detected early and addressed without delay, and any impact on benefit risk ratio can be quickly identified and assessed. This protocol is designed to investigate the safety of molnupiravir using a cohort event monitoring methodology.

Objectives: The overall aim of this observational study is to monitor the safety of molnupiravir for the purpose of safety signal detection. The specific objectives include:

Primary objectives

1. to characterize and estimate the incidence of all adverse events (AEs, including serious adverse events (SAEs), medication errors, off-label use and misuse) occurring in enrolled patients.

Secondary objectives

1. to characterize and estimate the incidence of maternal and perinatal outcomes in women inadvertently exposed to molnupiravir during pregnancy and neonate/infant/child exposed during breastfeeding;
2. to detect signals of drug-drug interactions and interactions with traditional medicines;
3. to estimate the incidence of severe COVID-19 disease following treatment with molnupiravir, to detect possible lack of adherence to treatment or lack of effect.

Study design: A multicentre multi-country observational, prospective, single-arm, cohort study for the active safety surveillance of molnupiravir that will be conducted in health facilities that provide molnupiravir to patients.

Study period: Study enrolmentwill start when the first authorized dose of molnupiravir is prescribed in the participating study sites. Enrolled patients will be actively followed-up for three months after their last dose. Pregnant women inadvertently exposed to molnupiravir will be followed until the end of the pregnancy and their children will be followed up until the age of 12 months.

Population: Participants will be recruited among patients who are prescribed molnupiravir for treatment of non-severe COVID-19 disease at sites participating in this study. Study participation will be strictly voluntary. Inclusion criteria: written informed consent and molnupiravir as per national policy. Exclusion criteria: patients unable to comply with study procedures.

Variables: Exposure to molnupiravir for COVID-19 treatment. The start date of treatment and dose will be recorded. Outcomes include all AEs, SAEs, and maternal and perinatal outcomes events. Information on concomitant medications, traditional medicine and supplements, non-adherence to treatment and progression to severe COVID-19 disease will be collected. Data will be collected at the start of the study, daily for the five days of molnupiravir treatment, five days after treatment, then monthly for three months after the last dose. Pregnant women inadvertently exposed to molnupiravir will be further followed up every three months (day (D)184 and D274) until the end of the pregnancy and the neonate/ infant will be followed up at birth and 6- and 12-months after birth.

Data sources: Data sources will include baseline information collected by study staff at recruitment, self-filled questionnaires (through mobile apps or Internet) or paper diaries, telephone survey or home visits by study staff. More than one type of data collection tool can be employed by study sites. A central hub will be set up to standardize the data collected, regardless of the tool used.

Sample size: The target study size is 30 000 patients treated with molnupiravir for COVID-19 disease. If no events are observed, this study size can rule out events occurring with a frequency of at least 1 per 10 000 with at least 95% confidence.

Data Analyses: Participation rates and demographic characteristics will be summarized using descriptive statistics. The mean and standard deviation, and median and range will be summarized overall and by age at enrollment, sex and country, when appropriate. Frequencies and percentages of outcomes will be provided by age group, sex and country when appropriate. Analyses of SAEs will include all patients. Frequencies and proportions of patients with identified SAEs will be calculated by time since start of therapy. A cumulative incidence will be calculated and plotted to visualize trends and identify inconsistent or /unexpected patterns. For proportions, 95% confidence intervals will be calculated using an exact method.

Periodic reporting: Interim analyses will be performed monthly.

Ethics This non-interventional study will be conducted in accordance with the international ethical guidelines for epidemiology studies published by the Council for International Organizations of Medical Sciences (CIOMS), the Declaration of Helsinki and its amendments, good epidemiological practice (GEP) guidelines and any applicable national laws and guidelines. Written informed consent will be obtained from all participating individuals. Data protection and privacy regulations will be strictly observed when capturing, forwarding, processing, and storing patients' data.

1. Background and rationale

In December 2019, the world witnessed an outbreak of respiratory disease caused by a novel coronavirus strain. The novel coronavirus was named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), while the disease associated with it is referred to as coronavirus disease 2019 (COVID-19). The virus spread to an increasing number of countries worldwide and on 30 January 2020 the World Health Organization (WHO) announced that the outbreak was a public health emergency of international concern (PHIC).

Molnupiravir has been newly introduced onto the market as the first oral medicine available for the treatment of non-severe COVID-19. Molnupiravir is a prodrug of the ribonucleoside analog β-D-N4-hydroxycytidine (NHC), which is phosphorylated in cells to form the pharmacologically active ribonucleoside triphosphate (NHC-TP) which then induces an antiviral effect via viral mutagenesis. WHO has provided a conditional recommendation for molnupiravir for those at highest risk of hospitalization. It is indicated for treatment of mild-to-moderate COVID-19 in adults (>18 years) with a positive SARS-COV-2 diagnostic test who have an estimated 10% increase in the risk of hospitalization. It is to be taken at a dose of 800 mg (four 200 mg capsules) orally every 12 hours for five days with or without food. The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available, and mitigation strategies include undertaking active pharmacovigilance surveillance.[1]

Although clinical trials show that molnupiravir is generally well tolerated[2 3 4 5 6 7 8 9], there are some concerns and unanswered questions about its safety. The main adverse events reported are dizziness, headache, diarrhoea, rash and urticaria. The main concerns are the potential mutagenic potential, teratogenicity in pregnancy and potential bone and cartilage toxicity. Authors of a study in animal cell cultures found mutations in cells treated with molnupiravir and recommend assessment of the mutagenic potential in host cell DNA with a focus on rapidly dividing cells.[10] There are no human pregnancy data currently, however, animal studies demonstrate fetal developmental abnormalities with molnupiravir exposure and therefore molnupiravir is not recommended for use during pregnancy. To minimize risks, women of childbearing potential should use effective contraception during the five days of treatment and for four days after.

Additionally, molnupiravir is contraindicated in patients younger than 18 years due to potential bone and cartilage toxicity.[11] There is also concern that molnupiravir's mutagenic potential could induce mutations in the SARS-CoV2 virus further leading to increased resistance.[12]

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