



Medicines & Healthcare products
Regulatory Agency



MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

National Procedure

Lagevrio 200 mg hard capsules

(molnupiravir)

PLGB 53095/0089

Merck Sharp & Dohme (UK) Limited

LAY SUMMARY

Lagevrio 200 mg hard capsules (molnupiravir)

This is a summary of the Public Assessment Report (PAR) for Lagevrio 200 mg hard capsules. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Lagevrio in this lay summary for ease of reading.

For practical information about using Lagevrio, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Lagevrio and what is it used for?

This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indication.

Lagevrio is used to treat mild to moderate COVID-19 (caused by SARS-CoV-2) in adults who are at risk for developing severe illness. Lagevrio may help people with COVID-19 stay out of the hospital and feel better.

How does Lagevrio work?

Lagevrio contains the active substance molnupiravir which is an antiviral medicine. Antivirals like molnupiravir work by keeping the viruses from multiplying within the body and stopping their spread so the immune system can deal with the virus more effectively.

How is Lagevrio used?

The pharmaceutical form of this medicine is a hard capsule and the route of administration is oral (via the mouth).

The patient should start Lagevrio within 5 days of the onset of COVID-19 symptoms.

How much to take

The recommended dose of Lagevrio is four 200 mg capsules, every 12 hours for 5 days.

How to take

- Swallow the capsule whole with plenty of fluid (for instance a glass of water).
- Do not open, break, or crush the capsules.
- This medicine can be taken with or without food.

For further information on how Lagevrio is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Lagevrio have been shown in studies?

Lagevrio has been studied in patients with mild to moderate COVID-19 who were at risk for progressing to severe COVID-19 and/or hospitalisation. Treatment with Lagevrio resulted in a 6.8% point reduction in the risk of hospitalisation or death (approximately 50% relative risk reduction) compared to placebo.

What are the possible side effects of Lagevrio?

For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the corresponding section of the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Coronavirus Yellow Card Reporting site at <https://coronavirus-yellowcard.mhra.gov.uk> or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Lagevrio (which may affect up to 1 in 10 people) are diarrhoea, nausea, feeling dizzy and headache.

Why was Lagevrio approved?

It was concluded that Lagevrio has been shown to be effective in the treatment of mild to moderate COVID-19 (caused by SARS-CoV-2) in adults who are at risk for developing severe illness. Furthermore, the side effects observed with use of this product are considered to be typical for this type of treatment. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Lagevrio has been authorised with a Conditional Marketing Authorisation (CMA). CMAs are intended for medicinal products that address an unmet medical need, such as a lack of alternative therapy for a serious and life-threatening disease. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon.

What measures are being taken to ensure the safe and effective use of Lagevrio?

A Risk Management Plan (RMP) has been developed to ensure that Lagevrio is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

The company has also committed to carry out further studies relating to patterns of use, bone marrow toxicity, emergence of viral variants, use in children and pregnancy. The company will also collect information on pregnancy outcomes in women exposed to Lagevrio during pregnancy through a suitable registry or study.

Other information about Lagevrio

A Marketing Authorisation for Lagevrio was granted in Great Britain (GB, consisting of England, Scotland and Wales) on 04 November 2021.

The full PAR for Lagevrio follows this summary.

This summary was last updated in December 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Lagevrio 200 mg hard capsules (PLGB 53095/0089) could be approved.

Lagevrio 200 mg hard capsules is indicated for treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness (see sections 4.2 and 5.1 of the SmPC for information on posology and limits of clinical trial population).

Molnupiravir is a prodrug that is metabolised to the ribonucleoside analogue N-hydroxycytidine (NHC) which distributes into cells where it is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP acts by a mechanism known as viral error catastrophe. NHC-TP incorporation into viral RNA by the viral RNA polymerase, results in an accumulation of errors in the viral genome leading to inhibition of replication.

This application was approved under Regulation 50 of The Human Medicines Regulation 2012, as amended (previously Article 8(3) of Directive 2001/83/EC, as amended), a full-dossier application. All non-clinical data submitted were from studies conducted in accordance with Good Laboratory Practice (GLP). All clinical data submitted were from studies conducted in accordance with Good Clinical Practice (GCP).

This application was evaluated as part of the rolling review licensing route. The rolling review process is intended to streamline the development of novel medicines. As part of the process the applicant submitted increments of the dossier for pre-assessment by the MHRA, rather than submitting a consolidated full dossier at the end of the product development process.

This product has been authorised as a Conditional Marketing Authorisations (CMA). CMAs are granted in the interest of public health and are intended for medicinal products that fulfil an unmet medical need and the benefit of immediate availability outweighs the risk posed from less comprehensive data than normally required. Unmet medical needs include, for example, treatment or diagnosis of serious and life-threatening diseases where no satisfactory treatment methods are available. CMAs may be granted where comprehensive clinical data is not yet complete, but it is judged that such data will become available soon. Adequate evidence of safety and efficacy to enable the MHRA to conclude that the benefits are greater than the risks is required, and has been provided for Lagevrio 200 mg hard capsules. The CMA for Lagevrio 200 mg hard capsules, including the provision of any new information, will be reviewed every year and this report will be updated as necessary.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-1000070-PIP01-21.

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 28 October 2021 on grounds relating to efficacy and safety. The CHM agreed, on the evidence before them, that the application could be granted albeit with conditions. The CHM advised the clinical indication should reflect the trial population without being too restrictive. The remaining uncertainties regarding safety in pregnancy and adverse effects on the foetus will be addressed through the RMP and other measures, which will be included in the conditions for the marketing authorisation (refer to section VI: Overall conclusion, benefit /risk assessment and recommendation for full details of these conditions).

A CMA was granted for this product in Great Britain on 04 November 2021.

II QUALITY ASPECTS

II.1 Introduction

Each hard capsule contains 200 mg of molnupiravir.

In addition to molnupiravir, this product also contains the following excipients:

Capsule content:

Croscarmellose sodium (E468), hydroxypropyl cellulose (E463), magnesium stearate (E470b) and microcrystalline cellulose (E460).

Capsule shell:

Hypromellose (E464), titanium dioxide (E171) and red iron oxide (E172).

Printing ink:

Butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol (E1520), purified water, shellac, strong ammonia solution and titanium dioxide (E171).

The finished product is packaged in high-density polyethylene (HDPE) bottles with a polypropylene closure containing 40 capsules. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

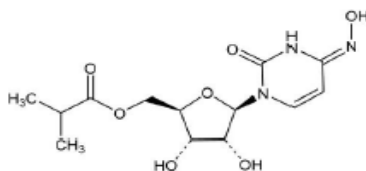
rINN: Molnupiravir (MK-4482, EIDD-2801)

Chemical Name: a. CAS Style Name: (4Z)-Uridine 4-oxime 5'-(2-methylpropanoate)

b. IUPAC Style Name: {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate

Molecular Formula: $C_{13}H_{19}N_3O_7$

Chemical Structure:



Molecular Weight: 259.22g/mol

Appearance: White to off-white powder

Solubility: Soluble in water, slightly soluble in ethyl acetate and acetonitrile, very slightly soluble in methyl tert-butyl ether, sparingly soluble in 2-propanol, freely soluble in methanol, and practically insoluble in n-heptane.

Molnupiravir is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

Confirmation has been given that the magnesium stearate used in the capsules is of vegetable origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. A process validation protocol and a commitment to complete process validation prior to commercialisation has been provided. This is acceptable.

Finished Product Specification

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 18 months, with the storage conditions 'This medicinal product does not require any special storage conditions. Store in the original package', is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

Molnupiravir (MOV) is an orally administered prodrug of a small molecule nucleoside [ribonucleoside analogue (beta-D-N4-hydroxycytidine [NHC])] with broad spectrum antiviral activity against a range of RNA viruses. It is being developed for the treatment of patients with COVID-19 and for prevention of COVID-19.

The non-clinical package (bibliographic and company data) comprise data to support the view that MOV has *in vitro* antiviral activity in mammalian cell-lines against a broad range of RNA viruses including coronaviruses (*e.g.*, SARS-CoV-2, SARS-CoV-1, and MERS-CoV). In addition, MOV antiviral activity is reported *in vivo* in animal models of MERS-CoV and SARS-CoV-1 infection. Furthermore, it is claimed that NHC is effective against remdesivir-resistant virus *in vitro*.

Rats and dogs were used for safety pharmacology and toxicology studies. MOV was devoid of effects on CNS, respiratory, or cardiovascular functions in well-characterised safety pharmacology models.

Biotransformation of MOV to NHC has been demonstrated. Since MOV biotransformation is faster in rodents compared to dogs and humans (*in vitro* plasma $t_{1/2}$ = 2 min rat; 3 h dog; 1.5 h human), the dog appears to be a better species for toxicity assessment of MOV. In line with the ICH M3(R2) guidance, the duration of the completed GLP repeated dose toxicity studies, 28 days both in rats and dogs, adequately supports the marketing authorisation application (MAA) based on an intended clinical posology in adult patients (800 mg Q12H for 5 days).

The non-clinical overview provides a summary of the non-clinical program, together with discussions of the findings and their clinical relevance.

All pivotal studies were carried out in compliance with Good Laboratory Practice (GLP) regulations, unless otherwise specified. In general investigations undertaken to establish suitable doses for use in the toxicity and pharmacokinetic studies were performed in accordance with the general principles of GLP.

III.2 Pharmacology

MOV is the 5'-isobutyrate prodrug of the broadly active, antiviral ribonucleoside analogue N-hydroxycytidine (NHC; formerly EIDD-1931). MOV is hydrolysed by esterases either during or after absorption to deliver NHC into systemic circulation. Once distributed inside cells, NHC is phosphorylated to its corresponding triphosphate anabolite (NHC-TP; formerly EIDD-2061), which inhibits replication by inducing viral error catastrophe. MOV inhibits replication of viral pathogens from multiple RNA virus families, including pathogenic coronaviruses (*e.g.*, MERS-CoV, SARS-CoV-1, and SARS-CoV-2), influenza viruses (seasonal, pandemic, and avian subtypes), RSV, alphaviruses (*e.g.*, EEEV, VEEV, and CHIKV), filoviruses (*e.g.*, Ebola virus), and ZIKV. Antiviral activity has been verified in animal models of coronavirus, influenza, RSV, VEEV, CHIKV, and Ebola virus infection.

The error catastrophe mechanism of action for NHC, has been validated for MERS-CoV, VEEV, and IAV. Multi-log decreases in virus yields and significantly increased levels of RNA mutations were observed when viruses were propagated in the presence of NHC. For VEEV, the infectivity of virions formed in the presence of NHC decreases from approximately 20% to <0.2%, and the infectious virions were significantly impaired in their replication ability. This mechanism of action makes the emergence of drug-resistant escape mutants less likely. This same effect, *i.e.*, decrease in infectious virions, was demonstrated for coronaviruses. NHC was also shown to be active against coronavirus resistant to remdesivir in cell culture assays.

Primary pharmacology studies demonstrating the antiviral activity of MOV against SARS-CoV-2 and other RNA viruses were conducted *in vitro* and in mouse, guinea pig, hamster, and ferret models of viral infection. *In vitro*, MOV shows broad-spectrum activity against multiple viruses including coronaviruses SARS-CoV-2, SARS-CoV, and MERS-CoV. NHC was active against coronaviruses that have mutations which reduce susceptibility to remdesivir in cell culture assays. Antiviral activity of MOV was also demonstrated in animal infection models of SARS-CoV-2, MERS-CoV, and influenza. MOV (500 mg/kg) significantly reduced infectious SARS-CoV-2 levels in lung tissue from LoM when administered 12 hours prior, 24 hours post, or 48 hours post direct infection of human lung tissue, followed by twice daily dosing thereafter. In a ferret model, treatment with MOV reduced SARS-CoV-2 infectious viral titres in nasal secretions from infected ferrets and suppressed all viral transmission to the untreated direct contacts, despite prolonged direct proximity between source and contact animals. In a Syrian hamster model of SARS-CoV-2 infection and disease, MOV prophylactic or therapeutic treatment showed decreased viral RNA titres and infectious virus from lungs several days post infection.

No inhibitory nature of clinical significance was reported following a non-GLP assay for inhibition potential against a panel of ion channels by NHC at 10 μM . Furthermore, in a separate study, neither MOV nor NHC exhibited $\geq 50\%$ inhibition at 10 μM against 107 of the 108 enzymes, receptors, or ion channels tested. MOV and NHC inhibited COX-2 with estimated IC_{50} values of >50 -fold its antiviral activity against SARS-CoV-2 in cell lines *in vitro* ($\text{EC}_{50} \leq 0.3 \mu\text{M}$) and is also above the clinical C_{max} (10.8 μM) at the human dose of 800 mg *q12h*. MOV IC_{50} is 243-fold above the MOV clinical C_{max} (0.026 μM) at the 800 mg *q12h* dose. These results indicated a low risk of off-target activity. The choice of concentration used in the inhibition study is justified. The concentration of 10 μM represents several-fold the NHC EC_{50} for antiviral activity against SARS-CoV-2 in various cell lines *in vitro* ($\text{EC}_{50} = 0.32$ to $2.66 \mu\text{M}$) and is ~ 385 the clinical C_{max} for MOV (0.026 μM) and is similar to the clinical C_{max} for NHC (10.8 μM) which has a short half-life of 1-1.3h. Follow up dose response assays for COX-2 inhibition by MOV and NHC demonstrated a 243-fold cover at the clinical C_{max} at the reported IC_{50} .

MOV was devoid of effects on CNS, respiratory, or cardiovascular functions in well-characterised safety pharmacology models. The rat and dog were selected for *in vivo* investigations based on the formation of the same metabolites as expected in humans. As no gender-specific pharmacokinetic (PK) differences have been observed in rat and dog toxicity studies, the use of males only in the cardiovascular, respiratory, and central nervous system (CNS) safety pharmacology studies were, therefore, acceptable. In line with the clinical route of administration, toxicology species were orally dosed.

The reported NOEL after a single oral dose in male rats for neuropharmacological and body temperature, effects was ≥ 500 mg/kg (NHC C_{\max} exposure 16-fold the NHC clinical C_{\max} value of $10.8 \mu\text{M}$ at the 800 mg *q12H* human dose (extrapolated from TK data for males from the 28 day toxicity study).

MOV: The hERG IKr currents were inhibited by $17.50 \pm 8.84 \%$ at $30 \mu\text{M}$. The IC_{50} value of MOV was estimated to be greater than $30 \mu\text{M}$ (>1000 -fold above the MOV clinical C_{\max} [$0.026 \mu\text{M}$] at the 800 mg *q12H* dose). NHC: The IC_{50} value of NHC was greater than $300 \mu\text{M}$ (28-fold above the NHC clinical C_{\max} of $10.8 \mu\text{M}$ at the 800 mg *q12H* dose).

In telemetered conscious dogs, the NOEL after a single oral dose (MOV) for cardiovascular and BT effects was ≥ 17 mg/kg (1.4-fold the NHC C_{\max} value of $10.8 \mu\text{M}$ at the 800 mg *q12H* human dose, (extrapolated from the TK data for males in the 28-day toxicity study in dogs).

In a separate study conducted at the higher single dose of 50mg/kg, there were no test article-related clinical signs nor test-article related changes in the parameters tested (BP/HR/BT/QT/QTci/QT:RR). The NOEL after a single oral dose in conscious, adult, telemetered beagle dogs for cardiovascular and BT effects was ≥ 50 mg/kg (5-fold the NHC C_{\max} value of $10.8 \mu\text{M}$ at the 800 mg *q12H* human dose (extrapolated from the TK data for males in the 28-day toxicity study in dogs).

The pulmonary assessment of MOV in rats administered up to 500 mg/kg did not result in any test article related changes in respiratory rate, tidal volume, or minute volume. The reported NOEL was the highest doses tested. This equates to 16-fold the clinical C_{\max} value of NHC (extrapolated from TK data for males from the 28-day toxicity study in rats).

Finally, there was no impact on the *in vitro* antiviral activity of NHC against SARS-CoV-2 in two-drug combination studies with 3TC, abacavir, FTC, hydroxychloroquine, nelfinavir, remdesivir, ribavirin, sofosbuvir, or tenofovir.

In conclusion, MOV is being developed for the treatment of patients with COVID-19 and for prevention of COVID-19. The pharmacodynamic data supports the view that MOV is a novel, small molecule inhibitor of viral replication, with potent and selective *in vitro* and *in vivo* activity against members of multiple genetically diverse coronaviruses and other RNA viruses. Importantly, it appears that MOV inhibits the human pathogenic coronaviruses, MERS-CoV and SARS-CoV in multiple relevant human cell types and exhibits *in vivo* efficacy against several animal models of SARS-CoV-2, including for prophylaxis, treatment, and prevention of transmission, as well as SARS-CoV-1 and MERS.

From a non-clinical safety perspective, the risk for CNS, respiratory, or cardiovascular effects in the clinic is considered low at projected therapeutic exposures. Therefore, it is concluded that the overall non-clinical pharmacology profile of MOV supports the rationale for clinical development for the treatment of human SARS-CoV-2 infection.

III.3 Pharmacokinetics

MOV is a 5'-isobutyrate ester prodrug designed to be metabolised by serum/cellular esterases to deliver the nucleoside metabolite NHC into systemic circulation following oral administration. An extensive evaluation of the pharmacokinetics and metabolism of MOV and the nucleoside NHC, as well as the distribution and exposure of NHC-TP in tissues has been completed. Both rodent and non-rodent species including those used in toxicity studies (rat and dog) were chosen for these evaluations based on the availability of animal models to

evaluate antiviral activity of MOV *in vivo*.

Absorption

MOV is a 5'-isobutyrate ester prodrug designed to be rapidly metabolised by serum/cellular esterases to deliver the nucleoside metabolite NHC into systemic circulation following oral administration. Cleavage of MOV to NHC may occur during absorption, during hepatic first pass, or after reaching systemic circulation. NHC then distributes into cells via nucleoside transporters and is phosphorylated by host kinases to the active triphosphate NHC-TP. Acute circulating plasma exposure of NHC is dependent on the absorption of MOV and conversion to NHC, as well as the rate of NHC uptake into cells and further metabolism to NHC-TP (*i.e.*, higher NHC-TP in cells results in lower NHC in plasma). Oral dosing of MOV has been completed in mouse, rat, dog, ferret, and monkey. The bioavailability of NHC after MOV was orally administered in rats and dogs was 52% and $\geq 77\%$, respectively, at oral doses ranging from 30 to 300 mg/kg.

MOV appears to be absorbed in all animal species. While MOV was not detected in the plasma of rodent species, possibly due to the higher plasma esterase activity, the main metabolite NHC was detected in plasma and increased dose proportionally or more than dose proportionally in most of the studied animal species.

Distribution

After oral dosing in mice, rats, dogs, monkeys and ferrets, NHC and the intracellular active metabolite NHC-TP were detected in most tissues including lung tissue. In monkeys, the highest concentrations of NHC-TP were in spleen and then lung at 12-h post dose with the lowest levels detected in the brain. NHC plasma protein binding is negligible while MOV protein binding was not assessed as it is not stable in plasma which is acceptable.

Metabolism

Following oral administration of [^{14}C]MOV in rats and dogs, the total recovery of radioactivity in excreta was low as it is expected that the majority of the dose is retained in the body and incorporated in the endogenous nucleotide pools. In dogs, less than 10% of the dose was recovered from urine and faeces within 96 hours post-dose with NHC constitutes more than 90% of the circulating radioactivity at 2 h post-dose and only a small amount of cytidine and trace level of MOV detected in the plasma.

For *in vitro* metabolism, MOV was unstable in rodent and monkey plasma and relatively more stable in human and dog plasma possibly due to different esterase activities. MOV and NHC are widely taken up by tissue culture cells and they are converted to the pharmacologically active NHC-TP. In hepatocytes, MOV is extensively metabolised across all species through hydrolysis to NHC. Uridine was also a major metabolite detected in human hepatocytes with minor metabolites detected in all species such as cytidine-monophosphate and uridine-monophosphate.

The conversion of NHC to NHC-TP is dependent on cellular uptake and subsequent phosphorylation processes. These processes require energy and could be dependent on oxygen level.

Hypoxia is common in severe COVID-19 infection, however, it is unlikely for hypoxia to impact the metabolism of NHC to NHC-TP based on the near plateau of the exposure-response relationship at 800 mg Q12h for some virologic endpoints and a trend with reduction of hospitalisations rate.

Excretion

The *in vivo* excretion and mass balance of MOV were studied in rats and dogs. The mean total recovery of radioactivity in rats and dogs was low indicating that MOV was converted into metabolites which were further incorporated into the endogenous nucleotide pools.

Pharmacokinetic (PK) drug interactions

Based on the data submitted, MOV and NHC have low risk for drug-drug interactions (DDI) through either of drug metabolising enzymes or transporters. However, for the final conclusion with regard to the DDI risk, MOV and NHC concentrations used in these studies should be compared to the maximum plasma concentrations observed in the human clinical studies to ensure that these concentrations are within the limits recommended in the Guideline for investigation of DDI (when the human exposure data become available).

III.4 Toxicology

MOV was evaluated in single and repeated dose toxicity studies in mice, rats and dogs. The duration studied (up to 3 months) is appropriate to support the likely clinical posology (5 days).

Rat

In the rat 7 day DRF study the dose of 2000 mg/kg/day was associated with clinical signs of toxicity and significantly decreased body weights in males with changes in haematology parameters, including decreased RET count, white blood cell, and absolute lymphocyte counts. High-dose males had clinical chemistry changes that included slightly increased liver enzymes (ALT and AST). High-dose females showed only mild elevations of ALT, calcium, glucose, and inorganic phosphorus. The improved tolerability in females compared to males at 2000 mg/kg/day may be attributable to 1.4- to 3.4-fold lower exposures in females compared to males. Notably, in the 3-month study, there were no clinical pathology changes indicative of liver toxicity and no histomorphological liver findings up to the highest dose tested, 1000 mg/kg/day (x9.3 and x15 NHC exposure at the 800 mg q12H human dose, in females and males, respectively). Therefore, these findings are expected to be of low clinical relevance.

In the subsequent 28-day rat study, MOV doses up to 500 mg/kg for 28 days were generally well tolerated with only reversible increases in liver weights noted (12-17% relative to brain weight), and therefore, 500 mg/kg/d was assigned the NOAEL.

The main adverse effects noted in the 3-month rat study were bone and cartilage toxicity in the long bones (femur, tibia), in males at ≥ 500 mg/kg/day (x5.4 margin of exposure) and in females at 1000 mg/kg/day (x9.3 margin of exposure). These findings consisted of an increase in the thickness of the growth plate/physis, leading to decreased osteogenesis with variably decreased trabecular bone in the metaphysis in males at 1000 mg/kg/day and thickening of the subarticular cartilage in males and females at 1000 mg/kg/day. Minimal thickening of subarticular cartilage was observed in males at 500 mg/kg/day. Additional cartilage findings observed only in the 3-month toxicity study in rats included a minimal to mild cytoplasmic alteration in chondrocytes of the tracheal cartilage in males at ≥ 500 mg/kg/day.

The mechanism of action for the bone change is currently unknown. The applicant considers that the primary target organ is the growth cartilage of long bones (femur, tibia). The histomorphologic features of the changes observed in the bone were indicative of an

alteration in the normal physiologic progression of hypertrophic chondrocytes towards osteogenesis, resulting in impaired transformation of cartilage into new bone (endochondral ossification). It is important to note that the remaining tissues in the femorotibial joint, including the ligaments, synovial tissue, and other soft tissue, were unremarkable.

The bone and cartilage toxicity observed in the 3-month oral toxicity study in rats at ≥ 500 mg/kg/day (5.4-fold the clinical NHC AUC_{0-24hr} at the 800 mg Q12H dose) is of low risk for an indication in adult population, based on the following considerations:

- Physeal/epiphyseal growth cartilage is no longer present in the mature skeleton of adult humans whereas the 3-month toxicity study was conducted in rapidly growing rats (5- 6 weeks of age at study start) that approximately doubled their body weights over the study duration. In addition, the very rapid bone growth in rats cannot directly be translated to human due to species-specific differences in skeletal development and bone turnover. For example, longitudinal growth of long bones in rats at ages of 20- 60 days (i.e. 3-9 weeks, corresponding to a human age of approx. 2-14 years) is higher than in humans at ages of 2-8 years. The growth rate in rats was 375 $\mu\text{m/day}$ at an age of 20 days and 159 $\mu\text{m/day}$ at an age of 60 days, when measured in the proximal tibias, whereas the growth rate in humans (femur) was only 55 $\mu\text{m/day}$ at 2 years of age and decreased to 38 $\mu\text{m/day}$ at an age of 5 to 8 years.
- Bone/cartilage findings observed in rats manifested only after 3 months of treatment. There were no bone/cartilage findings in rats dosed for 1-month up to 500 mg/kg/day (4.2-fold (female) and 7.8-fold (male) the NHC exposure at the 800 mg Q12H human dose), in dogs dosed for up to 14 days at 50 mg/kg/day (1.6-fold the clinical NHC exposure at the 800 mg Q12H dose), or in WT CByB6F1 Tg(HRAS)2Jic mice dosed for 1 month up to 2000 mg/kg/day (19-fold the clinical NHC exposure at 800 mg Q12H).

The relevance for the paediatric population is unknown. An on-going study in juvenile rats (dosed from postnatal day 4) includes endpoints to inform the extent of bone and cartilage tissue affected, and the severity and reversibility of the changes.

Paediatric patients are not in the scope of the proposed indication. As detailed in the paediatric investigation plan (PIP), a study in juvenile rats will be completed before initiation of clinical investigations in paediatric patients. A PPND study in rats is on-going and is expected to be completed before end of 2021.

There were no findings or trends observed in the dog suggestive of bone or cartilage toxicity.

The rat bone/cartilage toxicity is described in the relevant sections of SmPC and the RMP to indicate that these findings are not relevant to adults and that the significance of these findings is unclear in the paediatric population in the event of off-label use. A recommendation to avoid breastfeeding for the duration of NHC systemic exposure is also included in the relevant section of the SmPC.

In the absence of a definitive conclusion on the clinical relevance of the findings relating to bone toxicity, the applicant has proposed juvenile toxicology and PPND studies prior to clinical trials in the paediatric population and has included warnings in the SmPC to mitigate

off-label use. This is accepted. Regarding the proposed population it is explained that the rapid growth in rats is not present in adults and the physal/epiphyseal growth cartilage is also absent in the developed adult. In the absence of studies on the mechanism of bone toxicity this provides some reassurance. Furthermore, exposure via breastmilk and to pregnant females is not recommended.

Dogs:

MOV was tolerated in dogs administered a single dose of up to 2000 mg/kg (no deaths, GI effects and weight loss/reduced food consumption). Subsequently 1000 mg/kg was selected as the high dose in the 7-day DRF study [Part B], however, doses of 300 and 1000 mg/kg/day exceeded the MTD due to mortality, clinical signs of toxicity and adverse clinical pathology changes noted at these doses. Body weight loss was observed from Day 5 (low dose). Dose-responsive, organ weight changes were noted most often in the reproductive organs as well as in the liver, spleen, and thymus of animals administered ≥ 300 mg/kg/day. No histopathology was conducted in this study. A NOAEL was not established.

The 28-day study in dogs included doses of up to 50 mg/kg/day and a 28-day recovery period. The NOAEL and MTD for this study were 6 mg/kg/day ($AUC_{last} = 9.53 \mu M \cdot hr$, 0.13-fold the NHC exposure at the 800 mg *q12H* human dose) primarily due to adverse bone marrow toxicity that affected all hematopoietic cell lines at ≥ 17 mg/kg/day (AUC_{last} of $\sim 30 \mu M \cdot h$ [Day 1], 0.4-fold the NHC exposure at the 800 mg *q12H* human dose). Hematologic changes were relatively mild at Day 7 with more severe changes apparent after 14 to 21 days of continuous dosing. The bone marrow changes were partially reversible or fully reversible following an approximately 1-week (for the 50 mg/kg/day group) or at least 1-month (17 mg/kg/day) recovery period, respectively. However, at these doses, animals could not tolerate dosing for 28 days as intended: Animals at 17 mg/kg/day received their last dose on Day 21 (males) or 22 (females). Animals at 50 mg/kg/day received their last dose on Day 12 or 14. No haematological effect was seen in rat.

Bone marrow toxicity is likely specific to dogs, dose and time dependent (>7 days). The proposed clinical treatment is 5 days, and there has been no indication of effects on peripheral blood cell count in the clinical programme thus far. Further monitoring is proposed in ongoing Phase III trials. In addition, dog bone marrow/haematological toxicity has been described in the relevant sections of SmPC and addressed in the RMP. This is acceptable.

Genotoxicity Assessment:

A complete battery of *in vitro* and *in vivo* genotoxicity studies, as per ICH S2(R1) guideline, has been carried out on MOV. Clear positive results were observed only in GLP bacterial mutation assay (Ames test) on the repair-proficient strain *Escherichia coli* WP2 *uvrA*, in presence and absence of rat liver S9 metabolic activation system. While the positive result in the presence of S9 mix makes the metabolite NHC responsible for mutagenicity, a direct mutagenic activity of MOV cannot be ruled out. *Escherichia coli* WP2 *uvrA* is a repair proficient strain able to detect DNA base substitution. Based on its mode of action (increase viral mutation rate), ribonucleotides like MOV/NHC, that escape from repair mechanism, can interfere with eukaryotic DNA replication and cause point mutations. However, this cannot be considered as a class effect for ribonucleoside analogue medicinal products. MOV was negative for inducing micronuclei in TK6 cells in the 4-hour treatments with and without metabolic activation and in the 27-hour treatment without metabolic activation under the conditions of this test system.

In line with CHMP scientific advice, the applicant conducted rat *in vivo* mutation assays (Pig-a mutagenicity assay and Big Blue® (cII Locus) transgenic rodent assay) as a follow-up to positive *in vitro* mutation assays, to gain further insight regarding the mutagenic potential of the candidate antiviral. The impact of MOV treatment on mutation rates was equivocal in the Pig-a assay rats when administered up to 500 mg/kg/day for 28 consecutive days. In accordance with the WHO/IPCS Harmonised Scheme on mutagenicity testing for chemical risk assessment, a second *in vivo* test was conducted as follow up to this equivocal *in vivo* mutagenicity result. The follow up *in vivo* assay chosen in this case was the Big Blue® Transgenic F344 Rat assay (cII locus) [OECD Test Guideline 488]. Mutation frequency was evaluated in a rapidly proliferating tissue, the bone marrow and a slowly proliferating tissue, the liver. MOV was not differentiable from mutation rates observed in untreated historical control animals. Furthermore, MOV was negative for induction of chromosomal damage in the *in vitro* (with and without metabolic activation) and *in vivo* rat micronucleus assays (no TK analysis). The minimal equivocal increased mutant frequency relative to vehicle control in the peripheral blood erythrocyte Pig-a mutation assay was not reproduced in the Big Blue® Transgenic F344 rat assay and hence the overall result from the *in vivo* mutagenicity assessment was considered negative. The applicant theorises that differences in metabolism, pharmacokinetics, exposure, replication, and DNA repair processes within a whole animal model compared with *in vitro* test conditions may account for the difference in results *in vitro* v *in vivo*. Based on the weight of evidence, it could be reasonable to assume that the positive mutagenicity findings do not translate *in vivo* and MOV is non-genotoxic.

Consistent with section 4.4 of the ICH S2 (R1) guideline, adequate exposure in the *in vivo* genotoxicity study in the Big Blue® Transgenic F344 Rat was demonstrated based on *in vivo* exposure data (toxicokinetic data) from the 7-day range-finding study in Fischer 344 male rats, using the same species, strain, and dosing route used in the genotoxicity assay. The lambda bacteriophage transgene carried by Big Blue® transgenic Fischer 344 rats is a neutral transgene not expected to affect Fischer 344 rat metabolism. In addition, the *in vivo* genotoxicity study in the Big Blue® Transgenic F344 Rat and the 7-day range-finding study in Fischer 344 male rats were conducted at the same test facility; the same lot of test article was used in both studies, and the formulations were prepared in the same way in the same vehicle.

Blood (for toxicokinetic assessment) was not collected from Big Blue® transgenic F344 rats used in the genotoxicity study in order to avoid confounding results of the genotoxicity assessment (e.g. by introducing multiple blood collections and associated stress) and to allow comparison of the results with historical control data from previous studies conducted using the same conditions at the test facility.

Based on toxicokinetic data from the 7-day range-finding study in Fischer 344 male rats, the high dose of 500 mg/kg/day in the *in vivo* genotoxicity study in the Big Blue® Transgenic F344 Rat was associated with NHC AUC_{0-24hr} exposure of 233 µM*hr (3-fold the human AUC_{0-24 hr} exposure at the 800 mg Q12H clinical dose) and C_{max} of 91.8µM (8.5-fold over the human C_{max} at the 800 mg Q12H clinical dose). Of note, 500 mg/kg/day is also the maximum tolerated dose given the decreased body weight gain (-21% compared to controls) and the clinical signs of hunched posture observed at this dose in the *in vivo* genotoxicity study. Overall, the results from the *in vivo* genotoxicity study in Big Blue® Transgenic F344 Rats dosed with MOV at exposures and duration exceeding the therapeutic target support the weight of evidence that MOV is not mutagenic or genotoxic in *in vivo* mammalian systems.

This study serves as a bridge to the absence of TK data in the Big Blue[®] Transgenic F344 Rat study. This is accepted, as the same rat strain; test facility and lot of test article was employed in both the genotoxicity study in question and the dose-range finding study cited. It is accepted that adequate exposure margins may be applicable in the genotoxicity study which supports the conclusion that MOV is not genotoxic in line with requirements of ICH S2 (R1).

Given the likely clinical posology (≤ 6 months dosing duration), the absence of carcinogenicity studies can be accepted.

Development and Reproductive Toxicity:

In male and female fertility studies, no effect on pregnancy, mating or fertility indices were noted at exposure levels that were comparable to x2.1 and x6.1 clinical NHC exposure levels at 800 mg *q*12H, in females and males, respectively. There were no MOV-related effects on embryonic development. At the time of this assessment NHC is not expected to adversely impact on fertility males or females.

In the preliminary embryofoetal development (EFD) study in rats, maternal toxicity included decreased food consumption and body weight loss, resulting in the early sacrifice of individual animals at 1000 mg/kg/day; developmental toxicity included embryoletality (post-implantation losses) and teratogenicity at 1000 mg/kg/day (7.5-fold the clinical NHC exposure at 800 mg *Q*12H), and reductions in foetal body weight at 500 mg/kg/day. In the definitive rat embryofoetal development (EFD) study, maternal toxicity, including overall decreased body weight gain and transient decreased food consumption; developmental toxicity (reductions in fetal body weight and numbers of ossified sacrocaudal vertebrae) was noted at 500 mg/kg/day. Based on these results, the NOEL/NOAEL for both maternal and developmental toxicity was 250 mg/kg/day (NHC AUC_{0-24h} = 58.3 μ M*hr, 0.8-fold the human AUC_{0-24h} exposure at 800 mg *q*12H).

In the definitive rabbit study, oral dosing of MOV to pregnant female rabbits resulted in mean plasma AUC levels of NHC slightly greater than dose proportional and mean plasma NHC C_{max} values generally dose proportional between MOV doses of 125 and 750 mg/kg/day. At the NOAEL for maternal (125 mg/kg/day) and developmental toxicity (400 mg/kg/day) clinical margins of exposure of x1.5 and x6.5 were determined for NHC. MOV-related maternal toxicity consisted of reduced mean body weight gain and associated reduced mean food consumption and abnormal faecal output at 750 mg/kg/day. There were no MOV-related effects on embryonic/foetal survival, foetal sex ratios, or foetal external, visceral, coronal, or skeletal morphology in any group. MOV-related reductions in mean live foetal body weights were seen in high-dose animals.

It is recommended for pregnant women not to use MOV and to advise women of childbearing potential to use contraception for the duration of NHC systemic exposure, given the teratogenicity and embryoletality observed in the preliminary embryofoetal developmental toxicity in rats at 7.5-fold the human NHC exposure at the 800 mg *Q*12H dose.

Phototoxicity:

Both MOV and NHC are not considered to be photoreactive. MOV and NHC have a low probability of being phototoxic in humans, and further phototoxicity testing is not warranted as per ICH S10 guideline.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

An acceptable Phase I ERA has been provided. The log Kow study is acceptable. A persistent, bioaccumulative and toxic (PBT) assessment is not required. The PEC_{SW} for molnupiravir is greater than the threshold of 0.01 µg/L and, therefore, a Phase II environmental effect analysis and risk assessment was submitted in October 2021.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

The following clinical studies were submitted with this application:

Table: Overview of Molnupiravir clinical studies:

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Status of Study Subject Exposure
MK-4482-004 (EIDD-2801-1001, P004)	I	UK, USA ^a	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers	Part 1: Double-blind, placebo-controlled single dose (randomized 3:1 active: placebo) Part 2: open-label randomized 2-period crossover FE study Part 3: Double-blind, placebo-controlled multiple dose (randomized 3:1 active: placebo)	Part 1: MOV 50, 100, 200, 400, 600, 800, 1200, 1600 mg or placebo single dose Part 2: MOV 200 mg single dose Part 3: MOV 50, 100, 200, 300, 400, 600, 800 mg or placebo Q12H × 5.5 days	Males/females (nonchildbearing potential), 18 to 60 years of age, healthy participants	Complete Part 1: MOV 50 mg: 6 MOV 100 mg: 6 MOV 200 mg: 6 MOV 400 mg: 6 MOV 600 mg: 6 MOV 800 mg: 6 MOV 1200 mg: 6 MOV 1600 mg: 6 Placebo: 16 Part 2: MOV 200 mg: 10 Part 3: MOV 50 mg: 6 MOV 100 mg: 6 MOV 200 mg: 6 MOV 300 mg: 6 MOV 400 mg: 6 MOV 600 mg: 6 MOV 800 mg: 6 Placebo: 14
MK-4482-005 (AGILE CST-2, P005)	I/2	UK	A Randomized, Multicenter, Seamless, Adaptive, Phase I/II Platform Study to Determine the Optimal Dose, Safety, and Efficacy of EIDD-2801 for the Treatment of COVID-19	Phase 1: Randomized, open-label, controlled versus standard of care Phase 2: Placebo-controlled, blinded (randomized 1:1)	Phase 1: MOV 300, 600, 800 mg BID × 10 doses Phase 2: 1:1 MOV 800 mg or placebo BID × 10 doses	Males/females, ≥60 years of age, or ≥50 years of age with ≥ 1 well controlled comorbidity, with PCR-confirmed SARS-CoV-2	

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Status of Study Subject Exposure
MK-4482-006 (EIDD-2801-2003, P006)	2a	USA	A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19	Randomized, double-blind, placebo-controlled	Part 1: 1:1 MOV 200 mg or placebo BID x 5 days Parts 2 to 9: 3:1 MOV up to 800 mg or placebo BID x 5 days	Males/females, ≥18 years of age with laboratory confirmed SARS-CoV-2	Enrollment Complete Part 1: MOV 200 mg: 23 Placebo: 23 Parts 2 to 9: MOV 400 mg: 62 MOV 800 mg: 55 Placebo: 39
MK-4482-007 (EIDD-2801-2004, P007)	2a	USA	A Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of EIDD-2801 on SARS-CoV-2 Virus Shedding in Newly Hospitalized Adults with PCR-Confirmed COVID-19	Randomized, double-blind, placebo-controlled		Males/females, ≥18 years of age, with PCR-confirmed SARS-CoV-2	

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Status of Study Subject Exposure
MK-4482-001 (MOVE-IN, P001)	2	Brazil, Canada, Chile, Colombia, France, Israel, Mexico, Philippines, Poland, Russia, South Africa, South Korea, Spain, Ukraine, UK, USA	A Phase 2/3 Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19	Randomized, placebo-controlled, double-blind	Part 1: 1:1:1:1 MOV 200, 400, 800 mg or placebo Q12H x 5 days Part 2: 1:1 selected dose of MOV or placebo Q12H x 5 days	Males/females, ≥18 years of age, with PCR-confirmed SARS-CoV-2, hospitalized	Enrollment complete Part 1: MOV 200 mg: 73 MOV 400 mg: 73 MOV 800 mg: 72 Placebo: 75 Part 2: will not be conducted
MK-4482-002 (MOVE-OUT, P002)	2/3	Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Japan, Mexico, Philippines, Poland, Russia, South Africa, Spain, Sweden, Taiwan, Ukraine, UK, USA ^c	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Adults with COVID-19	Randomized, placebo-controlled, double-blind	Part 1: 1:1:1:1 MOV 200, 400, 800 mg or placebo Q12H x 5 days Part 2: 1:1 selected dose of MOV or placebo Q12H x 5 days	Males/females, ≥18 years of age, with PCR-confirmed SARS-CoV-2, non-hospitalized	Enrollment complete Part 1: MOV 200 mg: 74 MOV 400 mg: 77 MOV 800 mg: 74 Placebo: 74 Part 2 Combined IA3/IA4 ^b : MOV 800 mg: 386 Placebo: 379 Part 2 ^d : As of 02-OCT-2021, 1433 participants enrolled

Study ID	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population	Status of Study Subject Exposure
^a One site in the UK enrolled all participants. No sites in the US enrolled participants. ^b IA4 was planned per protocol to occur after ~775 participants were randomized in Part 2 (the Phase 3 part of the study) and completed Day 29 follow-up. ^c Includes countries with sites that achieved Site Ready (SR) through Last Patient Last Visit (Day 29) in Part 1 and through Last Patient Last Visit (Day 29) for IA4 participants. ^d Upon review of the IA3/IA4 data, the study was closed to enrollment on 02-OCT-2021 at the recommendation of the eDMC and in consultation with the US FDA. BID=twice daily; COVID-19=coronavirus disease 2019; EIDD = Emory Institute for Drug Development; FE=food effect; IA4=interim analysis 4; ID=identification; MAD=multiple-ascending dose; MOV=molnupiravir (MK-4482, EIDD-2801); PCR=polymerase chain reaction; po = oral(ly); Q12H = every 12 hours RNA=ribonucleic acid; SAD=single-ascending dose; SARS-CoV-2=SARS-associated coronavirus-2; UK=United Kingdom; USA=United States of America							

All studies were conducted in line with current Good Clinical Practice (GCP).

IV. 2 Clinical Pharmacology

The clinical pharmacology evaluation of MOV is based on 4 clinical studies, a Phase 1 study (P004) in healthy participants and modelling analyses which included data from P004 and 3 Phase 2 studies in participants with COVID-19 (P001 [Part 1], P002 [Part 1], and P006).

P004 assessed the safety, tolerability and PK of MOV and NHC following single and multiple ascending doses of MOV. This study included a food effect assessment. One hundred thirty participants were enrolled; 100 received at least 1 dose of MOV and 30 received placebo. Single doses of MOV up to 1600 mg and multiple Q12H doses up to 800 mg for 5.5 days were evaluated.

Phase 1

Study P004

This was a randomised, double-blind, placebo-controlled, first-in-human study designed to evaluate the safety, tolerability, and pharmacokinetics of MOV following oral administration to healthy volunteers.

The study was composed of 3 parts; Part 1 was the single-ascending-dose study, Part 2 was the food-effect study, and Part 3 was the multiple-ascending-dose study.

Part 1: There were 8 dose-escalation cohorts (50, 100, 200, 400, 600, or 800 mg MOV (PIB formulation) or 1200 or 1600 mg MOV (capsule formulation), each of which comprised 8 subjects. Subjects were randomised to receive a single oral dose of either MOV or placebo on Day 1 in a 3:1 ratio; 6 subjects received MOV and 2 subjects received placebo.

Part 2: Subjects were randomised to a treatment sequence in a 1:1 ratio: 200 mg MOV (capsule formulation) in the fed state followed by 200 mg MOV (capsule formulation) in the fasted state or vice versa. There was a 14-day washout period between doses.

Part 3: There were 7 dose-escalation cohorts, each of which comprised 8 subjects. Subjects were randomised to receive either 50 to 800 mg MOV or placebo (capsule formulation) in a 3:1 ratio. Doses were administered twice daily (BID) on Days 1 through 5, inclusive, and a single final dose was administered on the morning of Day 6.

Results

- MOV was quantifiable in plasma following administration of MOV at higher doses; the geometric mean MRC_{max} (where measurable) ranged from 329 to 610 and <0.02% of the dose administered was excreted unchanged as MOV in urine.
- EIDD-1931 appeared rapidly in plasma following MOV dosing, with a median t_{max} between 0.500 and 1.5. hours for the PIB formulation and 1.00 to 6.00 hours for the capsule formulation.
- At lower doses (typically <800 mg), the elimination of EIDD-1931 was monophasic with a geometric mean $t_{1/2}$ of approximately 1 hour. A second, slower elimination phase was quantifiable at higher doses, with a geometric mean $t_{1/2}$ of 4.59 (range of 1.47 to 7.58 hours) following administration of a single 1600-mg dose of MOV and 7.08 hours (range of 1.49 to 19.1 hours) on Day 6 following multiple administrations of 800 mg MOV BID.
- Administration of MOV capsule formulation provided similar systemic exposure to EIDD-1931 (based on AUC_{0-inf} and AUC_{last}) as the PIB formulation at the same dose. However, C_{max} was up to 24% lower and t_{max} was up to 0.75 hours later following administration of the capsule formulation, indicating that the rate of absorption for the capsule formulation was slightly lower, but the extent of absorption was similar.
- Administration of MOV capsule formulation in the fed state delayed median t_{max} for EIDD-1931 by 2 hours and reduced C_{max} by 35.6% when compared to administration

in the fasted state. However, AUC_{0-inf} and AUC_{last} were similar (within 5%), which indicated that the rate, but not the extent, of absorption was lower in the fed state.

- Increases in AUC_{0-inf} and AUC_{last} for EIDD-1931 following administration of single doses of MOV and AUC_{τ} following administration of multiple doses of MOV were slightly supraproportional, particularly at higher doses. However, the increases in C_{max} were generally dose proportional.
- There was no evidence of accumulation, which was consistent with the dosing interval and the majority of $t_{1/2}$ estimates up to doses of 800 mg MOV BID. The longer secondary elimination phases observed for some subjects at 800 mg MOV BID did not result in consistently higher accumulation ratios as this phase represented only a small amount of the overall AUC_{τ} .
- Between-subject variability in systemic exposure to EIDD-1931 was generally low (<25%) to moderate (25% to 40%), but between-subject variability in urinary excretion parameters was generally high (>40%).
- The amount of EIDD-1931 that was excreted in urine was small and represented between 0.820% and 6.70% (geometric mean Fe0-24) of the dose administered following single doses of between 50 and 1600 mg MOV and between 0.854% and 3.61% (geometric mean Fe0-12) following multiple doses of between 50 and 800 mg MOV BID. There was a trend for the percentage of EIDD-1931 excreted in urine and CLR to increase with increasing dose at doses >200 mg.
- Overall, single doses of up to 1600 mg MOV or multiple doses of up to 800 mg MOV BID were generally safe and well tolerated, with fewer subjects reporting TEAEs following administration of MOV than placebo.

Phase 2

Study P006

This was a Phase IIa, double-blind, placebo-controlled, randomised trial designed to compare the safety, tolerability, and antiviral activity of escalating doses of molnupiravir vs placebo as measured by viral RNA detection, evaluation of adverse events (AEs), and other safety assessments, in symptomatic adult outpatients with COVID-19.

Up to approximately 172 fully evaluable participants were planned for enrolment into multiple study parts. If participants in a dose group dropped out or otherwise had missing or unevaluable primary or key secondary virology endpoint data, additional participants were enrolled to ensure adequate data at each dose level. The total number of participants to be enrolled was not to exceed 204.

Participants were randomised if they had signs or symptoms of COVID-19 within 7 days, and a positive SARS-CoV-2 RT-PCR within 4 days of enrolment. In Part 1 of this study, up to approximately 44 participants were randomised 1:1 to receive molnupiravir 200 mg twice daily (BID) (Arm A) or placebo BID (Arm B) orally for 5 days. Enrolment in Part 1 could be interrupted to initiate enrolment in a different cohort, and Part 1 enrolment could resume at a later time point. The study continued to enrol the following (optional) study parts:

- In Parts 2-4, up to approximately 16 participants per part were randomised 3:1 into Arms C and D (Part 2), Arms E and F (Part 3), and Arms G and H (Part 4) to receive treatment as follows: molnupiravir up to 800 mg or placebo orally BID for 5 days.
- In Parts 5-9, up to approximately 16 participants per part were randomised 3:1 into Arms I and J (Part 5), Arms K and L (Part 6), Arms M and N (Part 7), Arms O and P

(Part 8), and Arms Q and R (Part 9) to receive treatment as follows: molnupiravir up to 800 mg or placebo orally BID for 5 days.

The dose of molnupiravir evaluated in Part 1 was 200 mg BID. The doses selected for subsequent study parts could be the same, higher, or lower than the dose(s) studied in previous study parts, and could not exceed 800 mg BID. Doses were chosen based on emerging virology and safety data from this and other ongoing studies. Selected doses were communicated in an official memo/protocol clarification letter.

All planned study part sizes were approximate. Study parts could be combined for randomisation purposes if the same dose was planned for more than one part. Study parts enrolling at the same dose level could be enrolled simultaneously.

All participants were followed for 5 days on treatment and an additional 23 days off treatment at a series of in-clinic and in-home visits. Participants who did not start study treatment were replaced.

Nasopharyngeal swabs were analysed from 175 subjects at enrolment, Day 3, and Day 5 for SARS-CoV-2 infectivity. Culture medium was analysed for viral load at 2 and 5 days post-infection by RT-PCR.

Results

A total of 202 participants were randomised into the study and received at least 1 dose of double-blind study drug and 195 of those completed the study. The reasons that 7 participants did not complete the study included AE (n=2 randomised to molnupiravir and n=1 randomised to placebo), lost to follow-up (n=1 randomised to molnupiravir), physician decision (the investigator discontinued the participant because of lack of study drug compliance; n=1 randomised to molnupiravir), and withdrawal by subject (n=2 randomised to molnupiravir).

On average, participants in the molnupiravir 200 mg group were slightly younger, with a mean age of 36.5 years, compared with mean ages of 42.4, 42.2, and 39.7 years in the molnupiravir 400 mg, molnupiravir 800 mg, and placebo groups, respectively. The molnupiravir 800 mg group had the lowest mean viral load at Baseline at 5.80 log₁₀ copies/mL, compared with viral loads of 6.69, 6.38, and 6.11 log₁₀ copies/mL in the molnupiravir 200 mg, molnupiravir 400-mg, and placebo groups, respectively. The molnupiravir 800 mg group also had a higher proportion of Hispanic participants (60.0%) compared with the other treatment groups (range: 30.4% to 37.1%), while the molnupiravir 200 mg group had a higher proportion of black participants (13%) compared with the other treatment groups (range: 3.2% to 5.5%). Other demographic and Baseline characteristics were generally comparable across treatment groups.

Seventy-eight (45%) participants, median 4.62 days (min. 1.40, max. 7.54) from symptom onset, had a positive SARS-CoV-2 culture at enrolment (52 on active and 26 on placebo). The percentage of participants with a positive viral culture at enrolment who were positive on Day 3 was 20.4% on active and 28% on placebo (p = 0.56). At day 5, 24% of placebo participants were culture-positive compared to none treated with molnupiravir (p = 0.001).

	Molnupiravir 200 mg (N=23)	Molnupiravir 400 mg (N=61)	Molnupiravir 800 mg (N=53)	All Molnupiravir (N=137)	Placebo (N=61)
Primary Endpoint: Time to Undetectable SARS-CoV-2 RNA (days)					
Number (%) with response	21 (91.3)	48 (78.7)	49 (92.5)	118 (86.1)	49 (80.3)
Number (%) censored	2 (8.7)	13 (21.3)	4 (7.5)	19 (13.9)	12 (19.7)
Median time to response (95% CI)	22.0 (15.0, 28.0)	27.0 (15.0, 28.0)	14.0 (13.0, 14.0)	15.0 (14.0, 20.0)	15.0 (15.0, 27.0)
Log rank p-value	0.5551	0.7270	0.0128	0.4216	
Proportion of Participants with Undetectable SARS-CoV-2 RNA by Study Day					
Day 3					
Number (%) undetectable	2/23 (8.7)	6/60 (10.0)	11/53 (20.8)	19/136 (14.0)	6/61 (9.8)
p-value (Fisher exact test)	>.9999	>.9999	0.1199	0.4941	
Day 5					
Number (%) undetectable	5/23 (21.7)	15/59 (25.4)	16/53 (30.2)	36/135 (26.7)	8/61 (13.1)
p-value (Fisher exact test)	0.3304	0.1067	0.0373	0.0419	
Day 7					
Number (%) undetectable	4/23 (17.4)	16/58 (27.6)	22/52 (42.3)	42/133 (31.6)	17/61 (27.9)
p-value (Fisher exact test)	0.4051	>.9999	0.1173	0.7370	
Day 14					
Number (%) undetectable	12/23 (52.2)	31/59 (52.5)	38/51 (74.5)	81/133 (60.9)	40/61 (65.6)
p-value (Fisher exact test)	0.3166	0.1936	0.4095	0.6324	
Day 28 (EOS)					
Number (%) undetectable	21/23 (91.3)	45/55 (81.8)	46/48 (95.8)	112/126 (88.9)	46/56 (82.1)
p-value (Fisher exact test)	0.4924	>.9999	0.0343	0.2389	
Summary of SARS-CoV-2 Infectious Virus Results					
Day 1					
Number (%) positive participants	11/22 (50.0)	18/43 (41.9)	20/52 (38.5)	49/117 (41.9)	25/53 (47.2)
p-value (Fisher exact test)	>.9999	0.6816	0.4320	0.6167	
Day 3					
Number (%) positive participants	4/22 (18.2)	5/43 (11.6)	1/53 (1.9)	10/118 (8.5)	9/54 (16.7)
p-value (Fisher exact test)	>.9999	0.5691	0.0161	0.1225	
p-value (Exact Cochran-Armitage trend test)					0.0095
Day 5					
Number (%) positive participants	1/22 (4.5)	0/42 (0.0)	0/53 (0.0)	1/117 (0.9)	6/54 (11.1)
p-value (Fisher exact test)	0.6658	0.0335	0.0270	0.0043	
p-value (Exact Cochran-Armitage trend test)					0.0025
Day 7					
Number (%) positive participants	1/21 (4.8)	0/47 (0.0)	0/52 (0.0)	1/120 (0.8)	2/56 (3.6)
p-value (Fisher exact test)	>.9999	0.4990	0.4960	0.2379	
p-value (Exact Cochran-Armitage trend test)					0.092
MMRM Analysis of Change from Baseline in SARS-CoV-2 Viral Load					
Day 3					
	N=23	N=58	N=51	N=132	N=56
LSM Difference	0.064	-0.094	-0.203	-0.078	
p-value	0.7806	0.5891	0.2392	0.6108	
Day 5					
	N=23	N=56	N=52	N=131	N=57
LSM Difference	-0.150	-0.434	-0.547	-0.377	
p-value	0.5663	0.0300	0.0062	0.0347	
Day 7					
	N=23	N=51	N=49	N=123	N=56
LSM Difference	-0.076	-0.311	-0.534	-0.307	
p-value	0.7667	0.1168	0.0060	0.0896	
Day 14					
	N=23	N=53	N=48	N=124	N=54
LSM Difference	-0.019	0.026	-0.175	-0.056	
p-value	0.8932	0.8355	0.1258	0.6214	
Day 28 (EOS)					
	N=23	N=52	N=47	N=122	N=52
LSM Difference	-0.035	0.058	-0.044	-0.007	
p-value	0.5948	0.4147	0.4438	0.8911	

Table: Summary of qPCR Infectivity in participants with positive baseline cultures in Study P006

	Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	All Molnupiravir	Placebo
Category	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Day 1					
Number of Participants with Positive Infectivity	11/22 (50.0)	18/43 (41.9)	20/52 (38.5)	49/117 (41.9)	25/53 (47.2)
p-value ^a	>.9999	0.6816	0.4320	0.6167	
p-value ^b					0.3144
Day 3					
Number of Participants with Positive Infectivity	4/22 (18.2)	5/43 (11.6)	1/53 (1.9)	10/118 (8.5)	9/54 (16.7)
p-value ^a	>.9999	0.5691	0.0161	0.1225	
p-value ^b					0.0095
Day 5					
Number of Participants with Positive Infectivity	1/22 (4.5)	0/42 (0.0)	0/53 (0.0)	1/117 (0.9)	6/54 (11.1)
p-value ^a	0.6658	0.0335	0.0270	0.0043	
p-value ^b					0.0025
Day 7					
Number of Participants with Positive Infectivity	1/21 (4.8)	0/47 (0.0)	0/52 (0.0)	1/120 (0.8)	2/56 (3.6)
p-value ^a	>.9999	0.4990	0.4960	0.2379	
p-value ^b					0.092

The applicant concluded that this study met the objectives of showing an antiviral effect of molnupiravir and demonstrating the safety of molnupiravir in an adult outpatient population with mild to moderate COVID-19 disease. All efficacy and safety data accumulated during this study and analysis of the risk-to-benefit relationship for both safety and efficacy show that the molnupiravir 800 mg dose most quickly and effectively decreased levels of SARS-CoV-2 in patients with COVID-19 with no change in tolerability compared with lower doses. All virology data were consistent, regardless of whether virology endpoints were measured by SARS-CoV-2 RNA (RT-PCR) or culture of infectious virus. The proportion of participants who achieved nondetectable virus was higher in the molnupiravir 800 mg group. Molnupiravir did not inhibit the production of antibodies to SARS-CoV-2.

The applicant considered that the proposed mechanism of action of molnupiravir was supported by the results of next-generation sequencing analysis of SARS-CoV-2 RdRp. Furthermore, the faster reduction in viral load in the molnupiravir-treated groups compared with placebo among participants who did not have antibodies to SARS-CoV-2 at Baseline is indicative of a direct antiviral effect.

The tolerability and safety of all molnupiravir dose levels were comparable to placebo in all categories assessed. Overall, safety findings were identified in a smaller proportion of participants treated with molnupiravir compared with participants treated with placebo.

Based on the results of this study, continued development of molnupiravir at the 800-mg dose level has progressed.

Phase 2/3

One inpatient and one outpatient study were initiated:

- | | |
|---|--|
| <ul style="list-style-type: none"> • Patient Population: Adults (≥18 years) hospitalized with moderate or severe COVID-19 infection (but not ventilated), confirmed by RT-PCR & with symptom duration ≤10 days • Design: Randomized, double-blind study of MK-4482 vs. placebo • Dose/Duration: 200, 400, 800 mg vs. placebo BID for 5 days (Phase 2); final chosen dose vs. placebo (Phase 3) • Endpoint: Time to sustained recovery, defined as (1) not hospitalized; <u>OR</u> (2) hospitalized, not requiring supplemental oxygen & no longer requiring medical care • Sample Size: N=1300 (Phase 2: 300; Phase 3: 1000) • Conduct: 113 sites in 19 countries • Recruitment: Phase 2 enrollment complete; 304/1300 enrolled (last patient in on 11-Jan-2021); DBL 11-Mar-21 | <ul style="list-style-type: none"> • Patient Population: Symptomatic outpatient adults (≥18 years) with documented positive SARS-CoV-2 test result collected ≤7 days prior to study entry & with ≤7 days of symptoms of COVID-19 at entry • Design: Randomized, double-blind study of MK-4482 vs. placebo • Dose/Duration: 200, 400, 800 mg vs. placebo BID for 5 days (Phase 2); final chosen dose vs. placebo (Phase 3) • Endpoint: Hospitalization or death • Sample Size: N=1450 (Phase 2: 300; Phase 3: 1150) • Conduct: 103 sites in 17 countries • Recruitment: Phase 2 enrollment complete; 302/1450 enrolled (last patient in on 9-Jan-2021); DBL 11-Mar-21 |
|---|--|

Study P001

Data from the inpatient study (MOVE-IN) indicated that MOV is unlikely to demonstrate a clinical benefit in hospitalised patients, who generally had a longer duration of symptoms prior to study entry; therefore, the decision was made not to proceed to Phase 3.

Analysis of Time to Sustained Recovery Through Day 29
Modified Intent-To-Treat Population
MK4482-001 IA2

Treatment	N	Number of Events (%)	Person-day	Event Rate/100 Person-days	Median Time to Recovery ^a (days) (95% CI)	Recovery Rate at Day 29 in % ^a (95% CI)
MK-4482 200 mg	73	56 (76.7)	867.0	6.5	9.0 (7.0, 10.0)	81.5 (71.4, 89.7)
MK-4482 400 mg	73	56 (76.7)	788.0	7.1	9.0 (8.0, 10.0)	85.2 (75.4, 92.6)
MK-4482 800 mg	72	59 (81.9)	874.0	6.8	9.0 (8.0, 11.0)	84.3 (74.8, 91.6)
Placebo	75	61 (81.3)	896.0	6.8	9.0 (8.0, 11.0)	84.7 (75.5, 91.9)
Pairwise Comparisons					Hazard Ratio ^b (95% CI) ^b	p-Value
MK-4482 200 mg vs. Placebo					0.99 (0.68, 1.45)	0.5620 ^c
MK-4482 400 mg vs. Placebo					1.13 (0.78, 1.65)	0.3145 ^c
MK-4482 800 mg vs. Placebo					1.01 (0.69, 1.47)	0.4894 ^c
MK-4482 400 mg vs. MK-4482 200 mg					1.12 (0.76, 1.66)	0.3034 ^c
MK-4482 800 mg vs. MK-4482 200 mg					1.00 (0.69, 1.47)	0.4523 ^c
MK-4482 800 mg vs. MK-4482 400 mg					0.89 (0.61, 1.31)	0.6685 ^c

Study P002 (Phase 2)

Final results from the outpatient MOVE-OUT study showed numerically fewer participants in molnupiravir group were hospitalised or died compared to placebo. In addition, no infectious virus was recovered from any molnupiravir-treated participant by study day 5 and beyond, while some outpatients in the placebo group were culture positive up to day 10. It is stated that the largest overall magnitude of antiviral effect was observed in the 800 mg dose compared with the 200 mg and 400 mg doses. The differences in virology endpoints were more pronounced in participants enrolled < 5 days following symptom onset. The applicant concluded that the number of events reported were not sufficient to provide a meaningful measure of clinical effect, however benefit shown in subgroup analyses supports potential benefit for treatment. Therefore, the phase 3 trial inclusion criteria have been amended to focus on early course of disease and patients with risk factors (e.g., advanced age > 60 years old, obesity, diabetes).

Part 2 (Phase 3) was initiated in May 2021. Participants were randomised 1:1 to receive either MOV 800 mg or placebo Q12H for 5 days and followed for primary efficacy evaluation through Day 29. The randomisation was stratified by time to symptom onset (≤ 3 days, > 3 days). Part 2 (Phase 3) of P002 was designed and powered to demonstrate the efficacy of MOV at the selected dose.

Interim analysis (IA) 3 was planned for when 30-50% of the planned enrolment were followed through to the Day 29 visit. This interim analysis was for the purposes of sample size re-estimation. IA4 was planned for when 50% were followed to Day 29. This interim analysis was for the assessment of efficacy, with early stopping for efficacy planned if the one-sided p-value for the primary endpoint is < 0.0092 .

The primary endpoint, incidence of hospitalisation or death through day 29, was analysed using the Miettinen & Nurminen method stratified by the randomisation strata.

A total of 775 participants (50% of the Phase 3 planned enrolment) were randomised and followed through the Day 29 visit by 10 September 2021. The clinical database was locked on 18 September 2021 to conduct the IA3 and IA4 protocol-specified interim analyses (combined into a single database lock). Results from IA3/IA4 demonstrated the clinical efficacy of MOV 800 mg. In addition, the IA4 safety analysis demonstrated that MOV is generally well tolerated in patients with COVID-19 and supports the favourable safety profile of MOV as presented in this application. Upon review of these results, the study was closed to further enrolment on 02 October 2021 at the recommendation of the external data monitoring committee (eDMC) and in consultation with the US FDA. As of 02 October 2021, 1433 participants had been enrolled.

In Part 2 (Phase 3), baseline demographic and disease characteristics were generally comparable for the MOV and placebo groups in the combined IA3/IA4:

- All randomised participants reported symptom onset within 5 days prior to randomization with approximately half of the participants having symptom onset ≤ 3 days prior to randomization.
- Most randomised participants ($>99\%$) had at least 1 risk factor for progressing to severe illness from COVID-19. The most common risk factors were obesity (BMI ≥ 30 , 76.5%), age >60 years (13.7%), and diabetes mellitus (13.5%).
- There were numerically more patients aged > 75 years in placebo group (13 vs 7).
- Severity of COVID-19 at baseline was moderate for 43.4% of participants and mild for 56.0% of participants (as determined based on standard protocol-defined definitions).
- Most participants (85.5%) had detectable SARS-CoV-2 RNA (NP sample) and 18.2% of participants had positive SARS-CoV-2 antibody results at baseline.
- The most common (self-reported by $>60\%$ of participants) signs and symptoms of COVID-19 present at baseline in Part 2 were cough, fatigue, muscle or body aches, headache, and nasal congestion.
- Of participants with SARS-CoV-2 viral sequence data available at the time of the database lock (277/775; 35.7%), the 3 most common SARS-CoV-2 genotype clades at baseline were 21H (Mu, 35.0%), 21A (Delta, 22.4%), and 20J (Gamma, 22.4%).

Choice of 800 mg Q12H dose

To further support the relationship between MOV dose and viral mutations, additional analyses were performed using next generation sequencing (NGS) data from samples in study P001 and P002 - Part 1 (Phase 2). The initial analysis was limited to post-baseline mutations present at a frequency of 2% or greater of the total NGS reads. A secondary analysis of the NGS datasets was

subsequently performed to explore the frequency of minor variants (0.4% to 10%) in MOV treated and placebo samples. For Nasopharyngeal (NP) and Oropharyngeal (OP) samples from study P002 (Part 1), inclusion of these low frequency variants revealed a clear linear dose relationship between the number of minor variants and MOV dose.

Table 1 Number of Minor Variants in SARS-CoV-2 RNA Genome Sequence by Visit and Dose: P002 Part 1 Nasopharyngeal Swabs

Visit	Placebo		MOV 200mg		MOV 400mg		MOV 800mg		P-value for Linear Trend
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	
Day 1	37	6.6 (4.4, 9.9)	36	6.7 (4.4, 10.2)	36	6.0 (4.0, 9.1)	33	6.1 (3.9, 9.4)	0.7048
Day 3	35	12.5 (8.2, 19.1)	39	30.6 (20.5, 45.7)	37	47.4 (31.3, 71.6)	35	61.5 (40.3, 94.2)	<.0001
Day 5 (EOT)	24	20.6 (12.5, 34.0)	24	83.4 (50.5, 137.4)	20	129.1 (74.8, 223.4)	16	223.4 (121.6, 410.2)	<.0001

(*)Confidence interval: 95% based on maximum MOV/Molnupiravir. N= number of participants with available data.

Table 2 Number of Minor Variants in SARS-CoV-2 RNA Genome Sequence by Visit and Dose: P002 Part 1 Oropharyngeal Swabs

Visit	Placebo		MOV 200mg		MOV 400mg		MOV 800mg		P-value for Linear Trend
	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	
Day 1	22	12.0 (7.3, 19.5)	22	8.3 (5.1, 13.5)	17	8.7 (5.0, 15.5)	17	9.3 (5.3, 16.6)	0.5583
Day 3	19	14.6 (8.6, 25.1)	20	37.3 (22.2, 63.1)	15	51.6 (28.3, 93.3)	15	113.0 (61.9, 204.2)	<.0001
Day 5 (EOT)	12	22.8 (11.6, 44.7)	14	116.7 (62.7, 218.8)	8	59.4 (26.1, 134.9)	5	223.9 (79.1, 631.0)	0.0020

(*)Confidence interval: 95% based on maximum MOV/Molnupiravir. N= number of participants with available data.

Development of resistance

Resistance selection experiments with SARS-CoV-2 in cell culture are currently underway and results are expected in 4Q 2021. Based on available NGS data from the P001 and P002 (Part 1) studies, no MOV treatment-emergent resistance mutations in the viral polymerase have been identified in clinical trials to date. Resistance surveillance is proposed as part of the RMP.

Platform Trial

Study P005 (AGILE)

AGILE is a multicentre, multi-arm, multi-dose, multi-stage open-label, adaptive, seamless phase I/II Bayesian randomised platform trial to determine the optimal dose, activity and safety of multiple candidate agents for the treatment of COVID-19.

This study allows for the assessment of many candidates at different doses, with the ability to add candidates as they are identified or drop them as their evaluation is completed. Promising candidates will move to an external trial for further evaluation in the phase II/III setting.

Each candidate will be evaluated in its own trial, randomising between candidate and control with 2:1 allocation in favour of the candidate. Each dose will be assessed for safety sequentially in cohorts of 6 patients. Once a phase II dose has been identified efficacy will be assessed by seamlessly expanding into a larger cohort.

For molnupiravir (CST-2): Open-label 2:1 randomised controlled phase I trial of MOV versus standard of care to confirm the optimal dose, followed by a 1:1 blinded controlled parallel group Phase II trial of MOV versus placebo to test for efficacy.

Results from part 1 of the study are in the public domain as a pre-print on MedRxiv; *“Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase 1 dose-escalating, randomised controlled study”*.

<https://www.medrxiv.org/content/10.1101/2021.05.03.21256309v1.full.pdf>

This was a dose-escalating, open-label, randomised-controlled (standard-of-care) Bayesian adaptive phase I trial at the Royal Liverpool and Broadgreen Clinical Research Facility. Participants (adult outpatients with PCR-confirmed SARS-CoV-2 infection within 5 days of symptom onset) were randomised 2:1 in groups of 6 participants to 300 mg, (the planned 400 mg dose was skipped following review by the Safety Review Committee), 600 mg and

800 mg doses of molnupiravir orally, twice daily for 5 days or control. A dose was judged unsafe if the probability of 30% or greater dose-limiting toxicity (the primary outcome) over controls was higher than 25%. Secondary outcomes included safety, clinical progression, pharmacokinetics and virologic responses.

Of 103 volunteers screened, 18 participants were enrolled between 17 July and 30 October 2020.

Molnupiravir was well tolerated at 300, 600 or 800 mg doses with no serious or severe adverse events. Overall, 4 of 4 (100%), 4 of 4 (100%) and 1 of 4 (25%) of the participants receiving 300, 600 and 800 mg molnupiravir respectively, and 5 of 6 (83%) controls, had at least one adverse event (AE), all of which were mild (\leq grade 2). The probability of $\geq 30\%$ excess toxicity over controls at 800 mg was estimated at 0.9%.

Based on these results, the applicant concluded that molnupiravir was safe and well tolerated and a dose of 800 mg twice-daily for 5 days was recommended for Phase II evaluation. Inclusion criteria for the next phase have been modified to include subjects with at least one concomitant morbidity.

IV.3 Clinical efficacy & IV.4 Clinical safety

Efficacy results

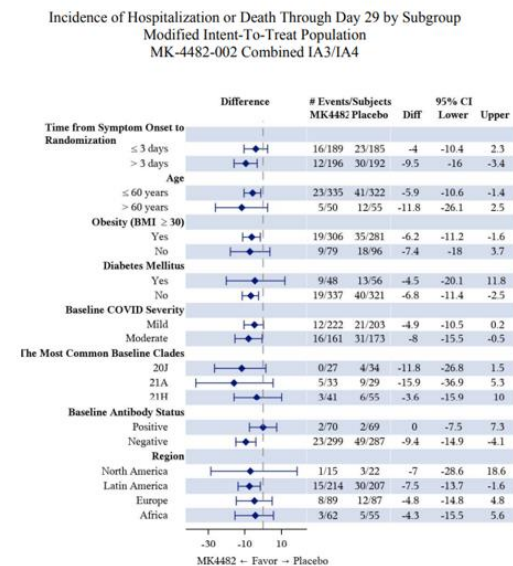
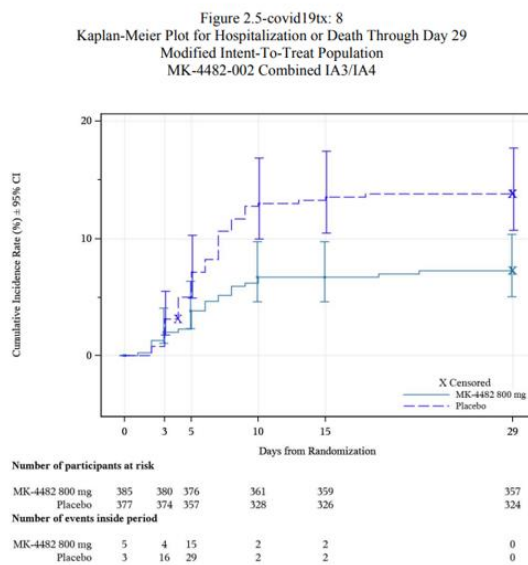
Study P002

Hospitalisation or Death Through Day 29 (Primary Endpoint)

The percentage of participants who were hospitalised or died through Day 29 in the MOV group, 28 (7.3%) was statistically significantly lower than in the placebo group, 53 (14.1%). Treatment with MOV resulted in a 6.8 percentage point reduction [95% CI: -11.3, -2.4; one-sided $p=0.0012$] in the risk of hospitalisation or death through Day 29 compared with placebo (approximately 50% relative risk reduction). MOV met the protocol-defined criterion (one sided p -value boundary <0.0092 at the IA4 timepoint) for demonstration of superiority to placebo for the primary efficacy endpoint.

There were no patients in the MOV group who died through day 29, while 8 (2.1%) died in the Placebo group. While not a planned test, this would have been statistically significant and satisfied the interim analysis stopping criteria (statistical assessor's calculation using Fisher's exact test).

Sensitivity and sub group analysis results were consistent with the above results except for the subgroup of participants positive for SARS-CoV-2 antibodies at baseline (representing approximately 18% of patients in each treatment group; suggesting recent or prior SARS-CoV-2 infection)- there was no difference between intervention groups in the percentage of participants who were hospitalized or died in this sub-group (2.9% in both groups).



Secondary endpoints

Symptoms of Covid-19 were self-reported by patients on a daily symptom diary, 15 symptoms of Covid-19 were evaluated at baseline and days 3, 5, 10, 15 and 29. These included fever, muscle ache, fatigue, sore throat, shortness of breath, nasal symptoms, cough, loss of smell/taste, chills etc. There were small numerical differences between the two groups for the number of patients with symptoms of Covid-19 at the different time points up to day 29, but generally the numbers were similar, with a reduction of all symptoms over the course of the disease in the placebo group too. Shortness of breath and fatigue until day 15 were absent in higher percentage of subjects on MOV than placebo, although by day 29, approximately 90% patients in both groups reported no shortness of breath.

Disease severity based on the WHO 11-point scale also reflected the above, with more patients in the higher categories in the placebo group compared to MOV between days 5 and 15.

Virologic Response (Exploratory Endpoints)

At the time of the database lock for IA3/IA4, testing for evaluation of virologic response was ongoing. Results from qualitative and quantitative SARS-CoV-2 RNA PCR for most participants are available through Day 10 and are presented in this application; fewer data are currently available for the later time points (Days 15 and 29). Post baseline SARS-CoV-2 viral sequence data are limited; available results from 92 participants (n=42 MOV; n=50 placebo) with both baseline and post baseline data have been included with this submission. Data for SARSCoV- 2 viral infectivity are very limited, precluding presentation of meaningful results for participants in P002 Part 2 at the time of this application.

SARS-CoV-2 RNA

Treatment with MOV was associated with a greater reduction in SARS-CoV-2 RNA from baseline compared with the placebo group at Days 3 and 5; results at other timepoints (Days 10, 15, and 29) were generally comparable between groups. After adjusting for baseline RNA titer, mean SARS-CoV-2 viral RNA titers were lower at Days 3 and 5 in the MOV group compared with the placebo group. The adjusted mean difference in SARS-CoV-2 RNA (in log10 scale; MOV minus placebo) was -0.24 at Day 3 and -0.44 at Day 5, which corresponds

to a 42% and a 64% relative reduction in the geometric mean SARS-CoV-2 RNA titer for the MOV group compared with the placebo group, respectively.

The percentage of participants who achieved undetectable SARS-CoV-2 RNA in NP samples by qualitative PCR was comparable for both intervention groups at various timepoints through Day 29, overall and regardless of baseline SARS-CoV-2 RNA titer ($>10^6$ and $\leq 10^6$ copies/mL).

Mutation Analyses

Consistent with the proposed mechanism of action for MOV (viral error catastrophe), treatment with MOV was associated with a higher mutation rate across the viral genome compared with placebo (7.4 [10.1] vs 3.4 [6.4]) among participants with paired baseline and Day 5 SARS-CoV-2 viral sequences.

Mutations occurring in the viral genome were further characterised by determining the frequency of specific nucleotide transitions and transversions in Day 5 sequences compared with baseline sequences.

- Higher mean numbers of C to U, G to A, and A to G transition mutations were observed in samples from participants in the MOV group (6.6, 3.6, 2.2) compared with placebo (4.1, 0.4, 0.5).
- Mean numbers of transversion mutations were low in both groups (preclinical animal model studies also showed a higher number of transition mutations compared with transversion mutations in viral RNA recovered from MOV-treated animals infected with SARS-CoV-2).

Safety results

Exposure

A total of 765 non-hospitalised participants with COVID-19 received at least 1 dose of study intervention and were included in the APaT population (386 participants in the MOV group and 379 in the placebo group). Duration of exposure to study intervention was comparable with a mean duration (in each group) of 4.4 days. The majority (>93%) of participants received 9 or 10 doses of study intervention.

Adverse Events

The percentage of participants with at least 1 AE was comparable between the MOV and placebo groups (35.0% and 39.6% participants, respectively). The observed percentages of participants with SAEs and SAEs leading to discontinuation of study intervention were lower in the MOV group compared to placebo. AEs leading to death were zero in the MOV group compared with 8 (2.1%) in the placebo group. The most frequently reported AEs ($\geq 5\%$ of participants in either group) were COVID-19 (MOV 8.0%, placebo 14.8%) and COVID-19 pneumonia (MOV 4.9%, placebo 9.0%).

No participant in the MOV group had laboratory values that met the predefined ECI criteria for potential DILI or for platelet count of $<50,000$ cells/ μL . No evidence of hematologic toxicity was observed in participants who received MOV. Participants aged ≥ 65 years had higher rates of SAEs compared with participants aged <65 years in both intervention groups.

Clinical efficacy and safety discussion

Efficacy and safety data are available from 775 patients; data from the remaining 658 patients, who were enrolled between DBL for the IA3/4 through 02 October 2021 remain

blinded. Top-line clinical efficacy and safety results through Day 29 for all 1433 enrolled participants will be available by the end of December 2021, while the final CSR will be available in 1Q-2022 and is proposed to be submitted post-licensing. Full virologic data for all 1433 enrolled participants (including the 775 IA3/IA4 subset) will be provided as part of the final clinical study report (CSR). A subsequent update summarising the Late Follow-up Month 7 results will be available in 2Q-2022.

Regarding the pivotal phase 3 outpatient study P002, a nearly 50% reduction in the number of hospitalisations and death in the MOV arm compared to the placebo group was observed. As this primary endpoint met the pre-specified stopping criteria for success, further enrolment has stopped in the trial. There were no deaths through day 29 in the MOV arm, compared to 8 (2.1%) in the placebo group. No statistical analysis was presented for this endpoint, but it would have been statistically significant based on the statistical assessor's calculation.

The secondary endpoints, evaluating the many symptoms of Covid-19 self-reported by patients did not show a clear difference between the two groups. The percentage of patients with each symptom at different time points were similar, except for shortness of breath and fatigue, which were higher in the placebo group at day 5 and day 10, respectively, but by day 15-29, there was no difference. However, shortness of breath appears to be the leading factor for hospitalisation, and this is reflected in the number of patients seen on the WHO ordinal scale. This also correlates with the viral load, which is lower in the MOV group at Day 5 compared to baseline, but by day 15-29, the change in viral load from baseline is similar in both groups. Similarly, the adverse effects of the respiratory system (cough and respiratory failure) are higher in the placebo group. This difference at day 5 appears to be driving the results of the primary analysis, as in all other respects the difference between the two groups is marginal, if any, and generally by day 29, any difference has disappeared.

As per the inclusion criteria, nearly all participants (758, 99.5%) in the MITT population had at least 1 risk factor for severe illness from COVID-19: 609 (79.9%) had 1 risk factor, 114 (15%) had 2 risk factors, and 35 (4.6%) had 3 or more risk factors. 593/775 (76.5%) participants were obese (BMI ≥ 30 kg/m²) in all randomised participants. Obesity was the only risk factor for 500 (84.3%) of these participants. Of the remaining 93 participants, 75 (12.6%) had 1 additional risk factor, 15 had 2 additional risk factors and 3 (0.5%) had 3 additional risk factors. The majority of the patients (76.5%) were obese, with almost 14% having diabetes, 10% with serious heart condition and 14% aged over 60 years.

Vaccinated participants were excluded from study P002 as the vaccination would interfere with the evaluation of the risk of hospitalisation or death (as primary endpoint). Enrolled participants were tested for SARS-CoV-2 antibodies using the Roche Elecsys® Anti-SARS-CoV-2 nucleocapsid antibody assay. This qualitative assay detects total antibodies (including IgA, IgM, and/or IgG) to the SARS-CoV-2 nucleocapsid protein in human serum but does not detect antibodies to spike generated by vaccination; a single qualitative outcome of "yes/no" is reported across all antibodies. Given this assay format, it is not possible to distinguish between antibodies generated due to a current or recent infection versus a previous infection, which makes these results difficult to interpret. Thus, no conclusions can be drawn regarding expected differences in efficacy among unvaccinated individuals or those who have generated antibodies due to natural infection (previous infection or recent infection) or due to vaccination against SARS-CoV-2 infection.

The applicant states that no further DDI studies or bone marker evaluation will be undertaken. The non-clinical findings of bone dystrophy were observed only after a long duration of treatment, and hence the applicant does not consider the need for bone biomarker evaluation in any population. The reversibility of bone and cartilage findings (including an assessment of femur length and histopathologic evaluation) is being evaluated in juvenile rats.

The applicant states there is no evidence of haematologic toxicity in MOV clinical trials to date, and this toxicity has been observed in the dog only. The impact of genetic polymorphisms on safety of patients treated with MOV is therefore considered unlikely. In particular, it is considered unlikely that ITPase variants (affected by ribavirin) impact safety in patients treated with MOV.

No data is available on paediatric subjects; further studies are planned as agreed in the PIP.

The 800 mg Q12H dose for 5 days is the most studied dose and although lower doses have been evaluated with a less than convincing dose-response, the applicant's reasoning for the choice of this dose are acknowledged.

Safety and efficacy conclusion

The totality of the efficacy and safety data from Phase 1, Phase 2 and Phase 3 studies demonstrates an acceptable efficacy, safety and tolerability profile of MOV for the population of adult out-patients with mild to moderate COVID-19 who have at least one risk factor for developing severe illness.

In line with CHM advice, the clinical indication has been revised in the product literature (SmPC and PIL) to reflect the trial population without being too restrictive. The remaining uncertainties concerning safety in pregnancy and adverse effects on the foetus will be addressed through the RMP and other measures and are included in the conditions for the grant of the marketing authorisation application.

Updates on Study P005 and P007

The Phase 1/2 P005 (AGILE) study and the Phase 2a P007 (US) study are ongoing and remain blinded.

P005 is implementing an adaptive design to evaluate the safety and efficacy of MOV for the treatment of COVID-19 in outpatient adults.

P007 is assessing MOV in adults who have tested positive for SARS-CoV-2 infection via PCR and are hospitalised with a diagnosis of COVID-19 with symptoms ≤ 7 days. Planned enrolment is approximately 96 participants.

IV.5 Risk Management Plan (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional safety measures have been proposed:

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern:

Safety Concern	Risk minimisation Measures	Pharmacovigilance Activities
Important Identified Risks: None		
Important Potential Risks		
Bone marrow toxicity*	<p>Routine risk minimisation measures:</p> <p>Predclinical safety data (section 5.3 of the SmPC)</p>	<p>Routine pharmacovigilance activities</p> <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • MK-4482-P002 (MOVE-OUT, P002) • MK-4482-005 (AGILE) • PASS
Missing Information		
Safety in Pregnancy	<p>Routine risk minimisation measures:</p> <p>Pregnancy and Predclinical Safety section of the prescribing information (Sections 4.6 and 5.3 of the SmPC)</p> <p>"What you need to know before you take Lagevrio" section of the Package Leaflet: Information for the patient</p>	<p>Routine pharmacovigilance activities</p> <p>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</p> <ul style="list-style-type: none"> • Follow up pregnancy questionnaires* <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Pregnancy study*
Safety in Lactation	Routine risk minimisation measures:	Routine pharmacovigilance activities
	<p>Lactation section of the prescribing information (Section 4.6 of the SmPC)</p> <p>"What you need to know before you take Lagevrio" section of the Package Leaflet: Information for the patient</p>	
Use in paediatric patients*	<p>Routine risk minimisation measures:</p> <p>Instructions regarding Paediatric Use are in section 4.2 (Posology and Method of Administration/Special Populations) and section 5.1 (Pharmacodynamic Properties) of the SmPC.</p> <p>Bone and cartilage findings are described in the section 5.3 of the SmPC.</p>	<p>Routine pharmacovigilance activities</p> <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • Juvenile animal toxicity study • PASS (pending the results of the juvenile toxicology study and in the scope of a future paediatric indication)
Emergence of viral variants*	<p>Routine risk minimisation measures:</p> <p>Viral resistance is described in section 5.1 of the SmPC (Pharmacodynamic Properties/Resistance)</p>	<p>Routine pharmacovigilance activities</p> <p>Additional pharmacovigilance activities:</p> <ul style="list-style-type: none"> • MK-4482-P002 (MOVE-OUT, P002) • The objectives, design and feasibility of a study to further characterise missing information on 'emergence of viral variants' in patients treated with molnupiravir will be discussed and agreed with the MHRA after exploring suitable approaches.
*not in the EU RMP v0.1		

This is acceptable.

IV.6 Discussion on the clinical aspects

The grant of a conditional marketing authorisation is recommended for this application.

V USER CONSULTATION

The marketing authorisation holder has provided a commitment to commence the full user consultation study in accordance with legal requirements on the final version of the PIL and will submit the results to the MHRA by December 2021.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of this in the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness.

Lagevrio 200 mg hard capsules has been authorised with a Conditional Marketing Authorisation (CMA). The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

The grant or renewal that has been made is conditional upon the fulfilment of the following conditions by 03/11/2022, unless otherwise stated below (see 'Due date' column):

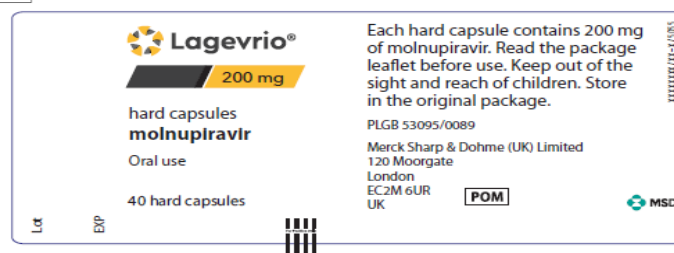
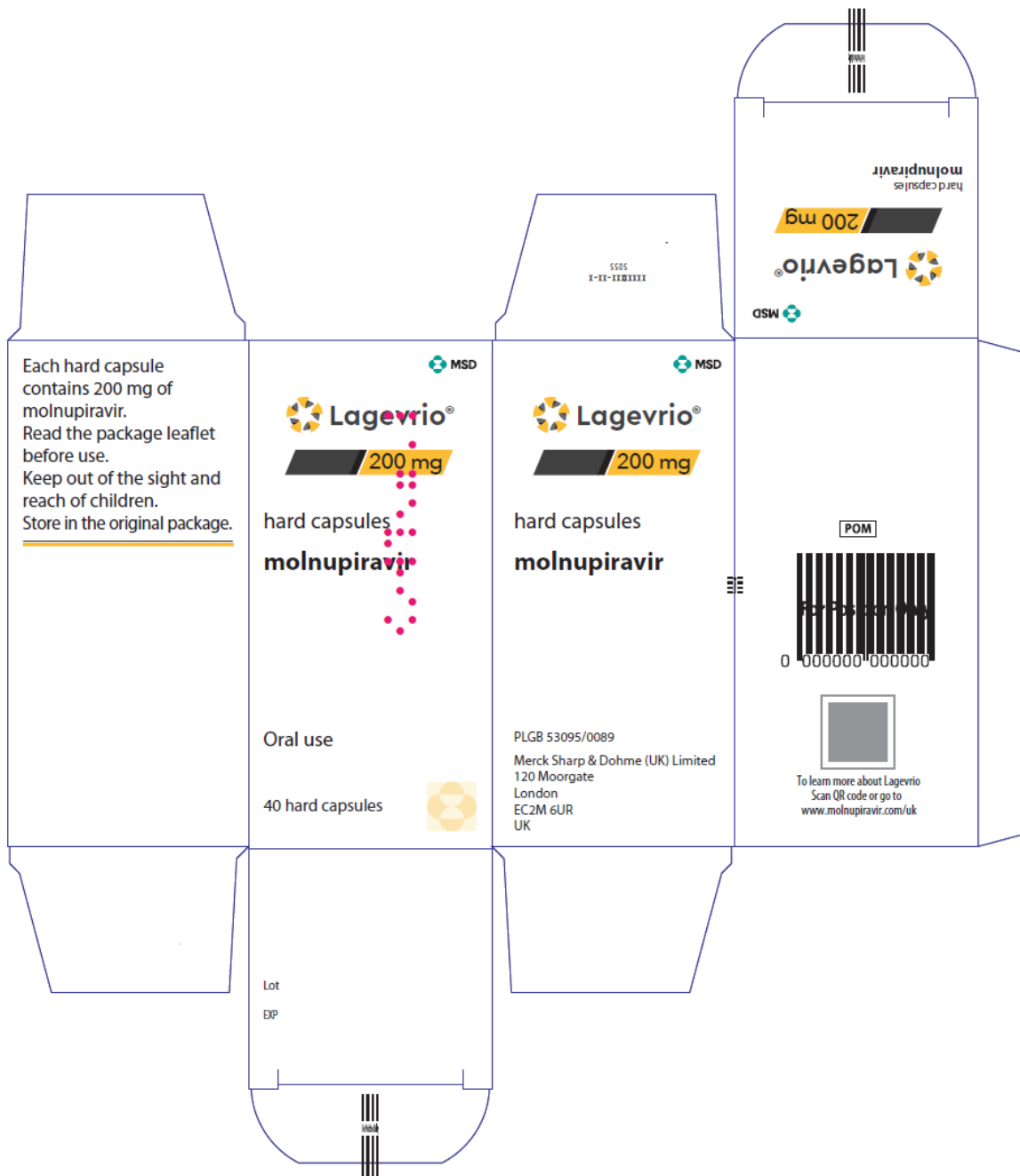
Description	Due date
1. The Company will provide the top line safety and efficacy results from the remaining 658 patients from study P002.	Estimated date by end of Dec 2021.
2. The Company will provide the final reports for submitted clinical study (P002), now submitted at the interim stage.	Estimated date by Q1 2022.
3. The Company will conduct the full PIL user test on the final version of the PIL and provide the results to the Agency.	Estimated date by end of Dec 2021.
4. The Company will add "use in paediatric patients" as missing information in a PLGB specific annex of the RMP and commit to updating this to reflect any issues of relevance that emerge from the Paediatric Investigation Plan, including providing data from the juvenile toxicology studies as per the plan. Approach to the further evaluation of the bone and cartilage findings through a PASS will be assessed pending the results of the juvenile toxicology study and in the scope of a future paediatric indication, after discussion with other regulators.	
5. The Company will commit to conducting a drug utilisation study to characterise use of molnupiravir. Study synopsis will be submitted following the Company's discussions with other regulators.	
6. The Company will add "emergence of viral variants" as missing information in a PLGB specific annex of the RMP along with proposals for monitoring further data on this topic. The Company will provide the complete virology analysis from the P002 Study, by end Q1 2022.	By end Q1 2022.
7. The Company will add "bone marrow toxicity" as an important potential risk to the PLGB specific annex of the RMP and will commit to provide an analysis of hematologic data from P002 based on updated results as described in Commitment 1. Estimated date by end of Dec 2021. Hematologic AEs will be included as AESI in the PLGB specific annex of the RMP and will be summarized in 6-month periodic safety reports. The objectives, design and feasibility of a PASS to address the important potential risk of "bone marrow toxicity" will be discussed and agreed with the MHRA after discussions with other regulators.	
8. The Company will commit to systematic collection of information on pregnancy outcomes in women exposed to molnupiravir during pregnancy through a suitable registry or study. It is anticipated that a study synopsis will be submitted within a 3-month time frame following approval of the conditional marketing authorisation.	
9. Good Laboratory Practice studies must be performed to standards in accordance with national regulations, relevant guidelines and the OECD Principles of Good Laboratory	

Practice. MSD (and its contracted parties) must accept GLP inspections by national competent authorities should such inspections take place.	
10. The Company must ensure that clinical trials are performed to national regulations and relevant guidelines including ICH GCP E6R2.	
11. The Company (and its contracted parties) must accept MHRA GPvP and GCP inspections to assess the compliance of any and all pharmacovigilance obligations and of the clinical trials and applicable data attached to the authorisation of the CMA and the supply of molnupiravir by virtue of regulation 174A. The powers of inspection will be the same as those outlined in regulations 325, 326 and 327.	
12. The Company will re-evaluate and, where appropriate, tighten the drug product shelf-life limits for the lower assay specification and total degradation products, when further additional manufacturing data becomes available.	Estimated date by Q4 2022.
13. The Company will test two representative batches of capsules stored in the bulk container for ~12 months under warehouse conditions and that any adverse trends in the data are immediately notified to the Licensing Authority with a course of action.	

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product is available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.



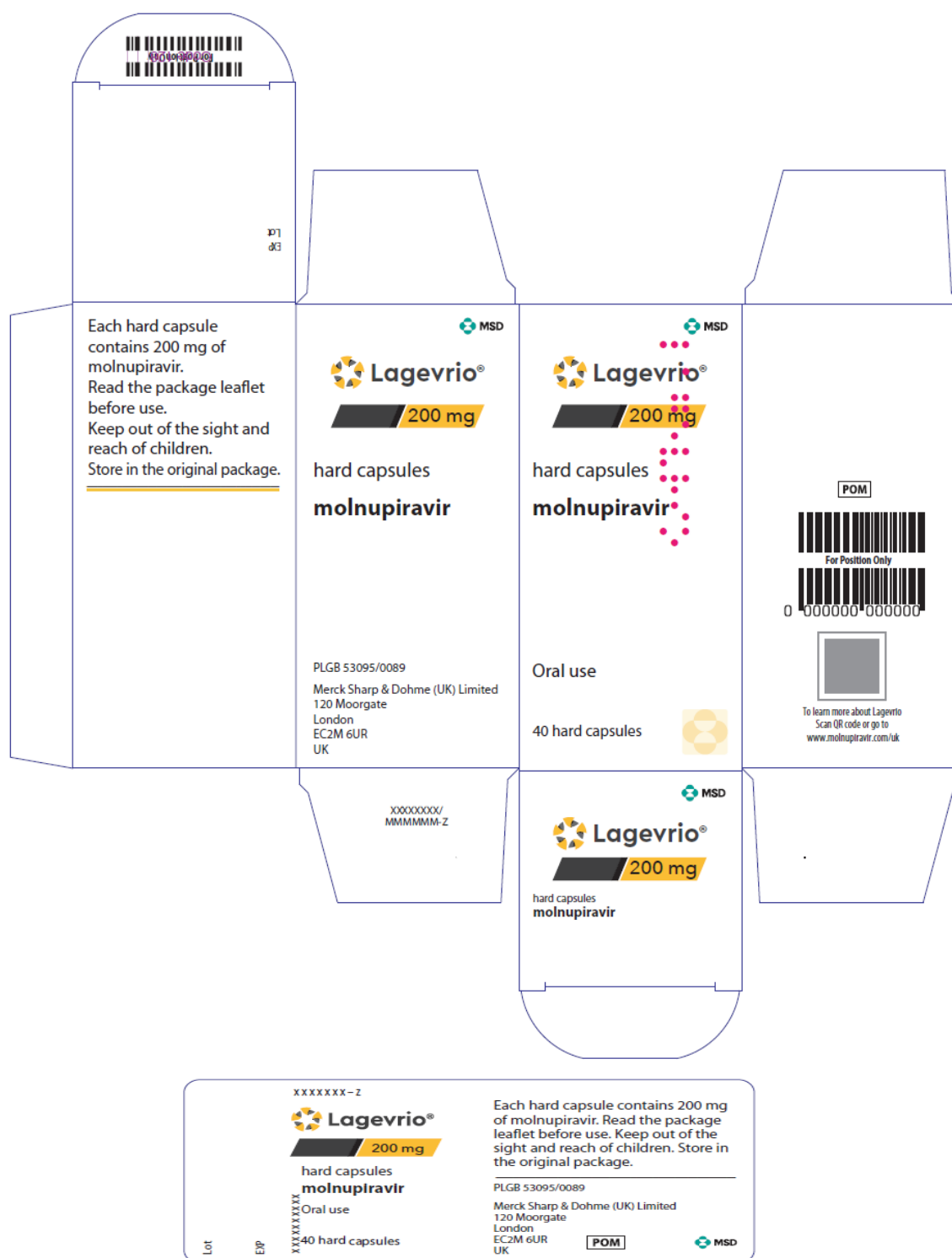


TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N