Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Molnupiravir

Proprietary Product Name: Lagevrio

Sponsor: Merck Sharp & Dohme (Australia) Pty Limited

February 2022

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ALT	Alanine transaminase
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AST	Aspartate transaminase
AUC	Area under the plasma concentration time curve
$AUC_{0\text{-}24hr}$	Area under the plasma concentration time curve from time zero to 24 hour
BMI	Body mass index
CD3	Cluster of differentiation 3
CD4	Cluster of differentiation 4
CDC	Centres for Disease Control and Prevention (United States of America)
CHO	Chinese hamster ovary
C_{max}	Maximum concentration
CMI	Consumer Medicine Information
COVID-19	Coronavirus disease 2019
DILI	Drug induced liver injury
DLP	Data lock point
ECI	Event of clinical interest
eGFR	Estimated glomerular filtration rate
EIDD-2801	Drug development code for molnupiravir
EMA	European Medicines Agency (European Union)
FDA	Food and Drug Administration (United States of America)
GD	Gestation day

Abbreviation	Meaning
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practices
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
IA	Interim Analysis
LLOQ	Lower limit of quantification
mITT	Modified intention-to-treat
MK-4482	Drug development code for molnupiravir
nCoV	Novel coronavirus
mRNA	Messenger ribonucleic acid
NHC	N-hydroxycytidine
OECD	Organisation for Economic Co-operation and Development
PASS	Post-authorisation safety studies
PCR	Polymerase chain reaction
PI	Product Information
PP	Polypropylene
PPND	pre- and post-natal development study
PSUR	Periodic safety update report
RdRp	Ribonucleic acid dependent ribonucleic acid polymerase
RHD	Recommended human dose
RMP	Risk management plan
RNA	Ribonucleic acid
rS protein	Recombinant spike protein
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event

Abbreviation	Meaning
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TK6	Thymidine kinase 6
T_{max}	Time at maximum concentration
US(A)	United States of (America)
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Lagevrio
Active ingredient:	Molnupiravir
Decision:	Approved for provisional registration
Date of decision:	18 January 2022
Date of entry onto ARTG:	20 January 2022
ARTG number:	372650
▼ *Black Triangle Scheme:*[1]	Yes. As a provisionally registered product, this medicine will remain in the Black Triangle Scheme for the duration of its provisional registration.
Sponsor's name and address:	Merck Sharp & Dohme (Australia) Pty Limited Level 1, Building A, 26 Talavera Road Macquarie Park, NSW 2113
Dose form:	Capsule
Strength:	200 mg
Container:	Bottle
Pack size:	40 capsules/bottle
Approved therapeutic use:	*Lagevrio (molnupiravir) has provisional approval for the treatment of adults with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk for hospitalisation or death (see Section 5.1 Pharmacodynamic properties - Clinical trials).* *The decision to approve this indication has been made on the basis of the analysis of efficacy and safety data from a Phase 3 trial. Continued approval of this indication depends on additional data.*
Route of administration:	Oral

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Dosage:	*Adult patients* The recommended dose of Lagevrio in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. The safety and efficacy of Lagevrio when administered for periods longer than 5 days have not been established. Lagevrio should be administered as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset in adults who are at risk for progression to severe COVID-19, including hospitalisation or death. Certain medical conditions or other factors may place individual patients at increased risk for progression to severe COVID-19 (see Section 5.1 Pharmacodynamic properties - clinical trials of the Product Information). *Paediatric patients* Safety and efficacy of Lagevrio have not been established in patients less than 18 years of age, therefore use in paediatric patients is not recommended (see Section 4.4 Special warnings and precautions for use - paediatric use and Section 5.2 Pharmacokinetic properties - special populations of the Product Information). For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Merck Sharp & Dohme (Australia) Pty Limited (the sponsor) to register Lagevrio (molnupiravir) 200 mg, capsule for the following proposed indication:

Molnupiravir is indicated for the treatment of COVID-19 in adults.

The World Health Organization (WHO) declared that the coronavirus disease 2019 (COVID-19) outbreak constituted a public health emergency of international concern on

30 January 2020,[2] and declared the outbreak to be a pandemic on 11 March 2020.[3] Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, positive sense, single stranded ribonucleic acid (RNA) betacoronavirus. COVID-19 is predominantly a respiratory illness that can affect other organs, patients with COVID-19 have reported a wide range of symptoms, include fever or chills; cough; shortness of breath; fatigue; muscle or body aches; headache; new loss of taste or smell; sore throat; congestion or runny nose; nausea or vomiting; and diarrhoea.

Since its emergence, SARS-CoV-2 has spread rapidly around the globe. As of 4 February 2022, there have been over 386 million confirmed cases of COVID-19 globally, with over 5.7 million deaths reported to the WHO.[4] In Australia, there have been over 2.3 million confirmed cases and 4,201 deaths reported as of 7 February 2022.[5] At the time of this report, the relevant public health units are struggling to contain outbreaks in Melbourne and in Sydney. This virus and the medical, social, and economic impact of the current pandemic is well known to the members of the community.

There are now a number of vaccines available in Australia to prevent COVID-19. These include Comirnaty (BNT162b2 (messenger ribonucleic acid (mRNA)), also known as the Pfizer/BioNTech vaccine;[6,7,8] the COVID-19 Vaccine AstraZeneca (ChAdOx1-S);[9,10] the COVID-19 Vaccine Janssen (Ad26.COV2.S);[11,12] Spikevax (elasomeran), also known as the Moderna vaccine;[13,14,15] and Nuvaxovid (SARS-CoV-2 recombinant spike (rS) protein with Matrix-M adjuvant).[16,17] Australia is in a fortunate position to have almost 93% of the

[2] World Health Organization (WHO) Statement on the Second Meeting of the International Health Regulations (2005) Emergency Committee Regarding the Outbreak of Novel Coronavirus (2019-nCoV), 30 January 2020. Available at: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov).

[3] World Health Organization (WHO) Director-General's Opening Remarks at the Media Briefing on COVID-19, 11 March 2020. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.

[4] World Health Organization (WHO), WHO Coronavirus (COVID-19) Dashboard, updated 14 January 2022. Available at: https://covid19.who.int/ (accessed 7 February 2022).

[5] Australian Government Department of Health, Coronavirus (COVID-19) Case Numbers and Statistics, updated 14 January 2022. Available at: https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-case-numbers-and-statistics (accessed 7 February 2022).

[6] Comirnaty was first registered on the ARTG on 25 January 2021 (ARTG number: 346290).

[7] AusPAR for Comirnaty (BNT162b2 (mRNA)) new biological entity, published on 25 January 2021. Available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna-comirnaty

[8] AusPAR for Comirnaty (BNT162b2 (mRNA)) extension of indications, published on 23 July 2021. Available at: https://www.tga.gov.au/auspar/auspar-bnt162b2-mrna

[9] COVID-19 Vaccine AstraZeneca was first registered on the ARTG on 16 February 2021 (ARTG number: 349072).

[10] AusPAR for COVID-19 Vaccine AstraZeneca (ChAdOx1-S) new biological entity, published on 16 February 2021. Available at: https://www.tga.gov.au/auspar/auspar-chadox1-s

[11] COVID-19 Vaccine Janssen was first registered on the ARTG on 25 June 2021 (ARTG number: 350150).

[12] AusPAR for COVID-19 Vaccine Janssen (Ad26.COV2.S) new biological entity, published on 25 June 2021. Available at: https://www.tga.gov.au/auspar/auspar-ad26cov2s

[13] Spikevax was first registered on the ARTG on 9 August 2021 (ARTG number: 370599).

[14] AusPAR for Spikevax (elasomeran) new biological entity, adult indication, published on 9 August 2021. Available at: https://www.tga.gov.au/auspar/auspar-elasomeran

[15] AusPAR for Spikevax (elasomeran) new biological entity, paediatric indication, published on 4 September 2021. Available at: https://www.tga.gov.au/auspar/auspar-elasomeran-0

[16] Nuvaxovid was first registered on the ARTG on 20 January 2022 (ARTG number: 355139).

[17] AusPAR for Nuvaxovid (SARS-CoV-2 recombinant spike (rS) protein with Matrix-M adjuvant) new biological entity, published on 21 January 2022. Available at: https://www.tga.gov.au/auspar/auspar-sars-cov-2-rs-matrix-m-adjuvant.

population aged 16 and over now vaccinated with 2 doses of an approved vaccine (as of 14 January 2022).[18]

The main management of COVID-19 in supportive with oxygen therapy and assisted ventilation as required. Medications that have been proven to be effective against COVID-19 and listed on the Australian Register of Therapeutic Goods (ARTG) include:

- Veklury (remdesivir), was provisionally registered;[19] on 10 July 2020 for the treatment of COVID-19 in adults and adolescents (aged 12 years and older, weighing at least 40 kg) with pneumonia, requiring supplemental oxygen.[20,21]

  The pivotal study was in 1,063 hospitalised patients. The recovery ratio was 1.47 in patients on oxygen.

- Xevudy (sotrovimab) was provisionally registered on 20 August 2021 for the treatment of adults and adolescents (aged 12 years and over and weighing at least 40 kg) with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk of progression to hospitalisation or death.[22,23]

  There were 1,585 participants (please note that vaccinated patients were excluded). Enrolment was stopped early as a prespecified interim analysis showed a 79% reduction in the risk of progression.

- Ronapreve (casirivimab/imdevimab) was provisionally registered on 18 October 2021 for the treatment of COVID-19 in adults and adolescents (aged 12 years and older and weighing at least 40 kg) who do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe COVID-19. Ronapreve is also indicated for the prevention of COVID-19 in adults and adolescents (aged 12 years and older and weighing at least 40 kg) who have been exposed to SARS-CoV-2 and who either: have a medical condition making them unlikely to respond to or be protected by vaccination, or are not vaccinated against COVID-19.[24,25]

  There were 4,567 patients in the clinical trial evaluating the efficacy of Ronapreve for the treatment of COVID-19. There was a 70% reduction in the risk of hospitalisation or death.

[18] Australian Government Department of Health, Vaccination Numbers and Statistics, updated 14 January 2022. Available at: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/numbers-statistics (accessed 16 January 2022).
[19] As part of the **provisional approval pathway**, the provisional registration process will allow certain medicines to be provisionally registered in the Australian Register of Therapeutic Goods (ARTG) for a limited duration. These medicines are registered on the basis of preliminary clinical data, where there is the potential for a substantial benefit to Australian patients. The TGA will re-assess risks related to the absence of evidence through data provided at a later stage, as part of the confirmatory data. Confirmatory data should confirm the relationship between outcomes predicted by the surrogate endpoint, or other preliminary data, and the clinical benefit as demonstrated by direct clinical outcomes.
The sponsor may apply to transition to full registration at any time up until the provisional registration lapse date, once they have completed the obligations outlined for the provisional registration period and complete confirmatory data on safety and efficacy are available.
[20] Veklury was first registered on the ARTG on 10 July 2020 (ARTG number: 338419).
[21] AusPAR for Veklury (remdesivir) new chemical entity, published on 21 July 2020.
Available at: https://www.tga.gov.au/auspar/auspar-remdesivir
[22] Xevudy was first registered on the ARTG on 20 August 2021 (ARTG number: 364110)
[23] AusPAR for Xevudy (sotrovimab) new biological entity, published on 20 August 2021.
Available at: https://www.tga.gov.au/auspar/auspar-sotrovimab
[24] Ronapreve was first registered on the ARTG on 18 October 2021 (ARTG number: 373839 and 374310)
[25] AusPAR for Ronapreve (casirivimab/imdevimab) new biological entity, published on 2 November 2021.
Available at: https://www.tga.gov.au/auspar/auspar-casirivimabimdevimab

- Actemra (tocilizumab) was provisionally registered on 2 December 2021 for the treatment of COVID-19 in hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.[26,27]
- Regkirona (regdanvimab) was provisionally registered on 6 December 2021 for the treatment of adults with COVID-19 who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19.[28,29]
- Paxlovid (nirmatrelvir/ritonavir) was provisionally registered on 20 January 2022 for the treatment of coronavirus disease 2019 (COVID 19) in adults 18 years of age and older, who do not require initiation of supplemental oxygen due to COVID-19 and are at increased risk of progression to hospitalisation or death.[30,31]

Molnupiravir (also known as EIDD-2801 or MK-4482) has a potential role in the treatment of patients who test positive for COVID-19, have symptoms of COVID-19 and are at high risk of severe disease. There is a high public interest in this medicine as it can be administered orally, and therefore more easily used in the community than the other therapies described above that need to be administered via intravenous infusion.

Molnupiravir is a prodrug of a small molecule nucleoside with broad spectrum antiviral activity against a range of RNA viruses. The primary mechanism of action is the inhibition of viral RNA replication by incorporation of the triphosphate metabolite into the viral RNA genome leading to 'viral error catastrophe'.

Following oral delivery, molnupiravir is rapidly hydrolysed by circulating esterases to produce high circulating plasma levels of EIDD-1931 (an active metabolite of molnupiravir) which is in turn absorbed by cells and phosphorylated into a triphosphate form (EIDD-2061) that is recognised by viral RNA dependent RNA polymerase (RdRp). EIDD-2061 can base pair with either guanosine or adenosine and can substitute for either cytidine triphosphate or uridine triphosphate, respectively, resulting in an accumulation of mutations that increase with each cycle of viral RNA genome replication. Additionally, the active metabolite, EIDD-2061 may act as a delayed chain terminator and arrest viral replication via a next nucleotide effect. Given this dual mechanism of action, it is anticipated that there will be a high barrier to the development of resistance.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the United Kingdom on 4 November 2021 and the United States of America (USA) on 23 December 2021. Similar applications were under consideration in the European Union (submitted on 21 October 2021), Canada (submitted on 13 August 2021) and Switzerland (submitted on 13 August 2021).

[26] Actemra was first registered on the ARTG on 21 May 2009 (ARTG number: 149402).
[27] AusPAR for Actemra (tocilizumab) extension of indications, published on 6 January 2022. Available at: https://www.tga.gov.au/auspar/auspar-tocilizumab-rch-3.
[28] Regkirona was first registered on the ARTG on 6 December 2021 (ARTG number: 374190).
[29] AusPAR for Regkirona (regdanvimab) new biological entity, published on 7 December 2021. Available at: https://www.tga.gov.au/auspar/auspar-regdanvimab.
[30] Paxlovid was first registered on the ARTG on 20 January 2022 (ARTG number: 377572).
[31] AusPAR for Paxlovid (nirmatrelvir/ritonavir) new chemical entity, published on 25 January 2022. Available at: https://www.tga.gov.au/auspar/auspar-nirmatrelvirritonavir.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United Kingdom	30 June 2021	Approved on 4 November 2021	*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.*
United States of America	8 October 2021	Emergency Use Authorization approved on 23 December 2021.	*Treatment of mild-to-moderate COVID-19 in adults with a positive result of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically* appropriate.
European Union	21 October 2021	Under consideration	Under consideration
Canada	13 August 2021	Under consideration	Under consideration
Switzerland	13 August 2021	Under consideration	Under consideration

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Data were provided as a rolling submission. Under normal circumstances, the TGA's assessment (for both provisional and general registration) begins once all information to support registration is available. As part of the Department of Health's response to the

pandemic, the TGA has agreed to accept rolling data for COVID-19 vaccines and treatments, to enable early evaluation of data as it comes to hand.

This application was evaluated under an Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) work-sharing agreement to allow for an expedited review of the submission.

Table 2: Timeline for Submission PM-2021-03679-1-2

Description	Date
Determination (Provisional)[19]	9 August 2021
Submission dossier accepted and first round evaluation commenced	17 August 2021
Evaluation completed	30 November 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	26 November 2021
Sponsor's pre-Advisory Committee response	1 December 2021
Advisory Committee meeting	3 December 2021
Registration decision (Outcome)	18 January 2022
Completion of administrative activities and registration on the ARTG	20 January 2022
Number of working days from submission dossier acceptance to registration decision*	104

*Statutory timeframe for standard applications is 255 working days

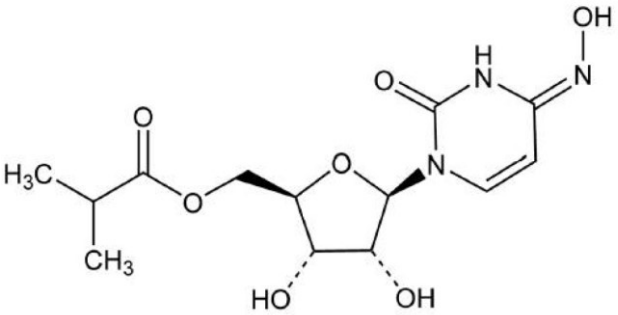
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Molnupiravir is an orally administered prodrug of a small molecule nucleoside with broad spectrum antiviral activity against a range of RNA viruses. The chemical structure for molnupiravir is given below:

Figure 1: Chemical structure of molnupiravir



The proposed administration of molnupiravir is 800 mg every 12 hours by oral administration for 5 consecutive days. The maximum daily dose is therefore 1600 mg/day.

The proposed product (molnupiravir capsules) are to be supplied in 60 cc white opaque high-density polyethylene (HDPE) bottles and polypropylene (PP) closure with heat induction seal liner, with a 33 mm child resistant cap. The sponsor provides satisfactory assurance that that the child resistant properties of the packaging are not affected by the contents and are retained throughout the product shelf-life, including during routine use.

Each bottle contains 40 molnupiravir capsules (representing a full 5-day regimen). The capsules are supplied as 'Swedish Orange' coloured, opaque, size 0 dry filled capsules with the corporate logo printed in white ink on one half and '82' printed in white ink on the other half.

Each Lagevrio capsule (the drug product) contains molnupiravir (as the active ingredient), and microcrystalline cellulose, hydroxypropyl cellulose, and croscarmellose sodium with purified water as inactive ingredients. The finished product was encapsulated in the hypromellose capsule shell.

The quality of the drug product is controlled by an acceptable specification that includes tests and limits for description, identification, assay, related substances, uniformity of dosage units, dissolution, and microbial content. The analytical methods used to analyse the product were adequately described and validated.

The stability data supplied support a shelf life of 18 months when stored below 30°C.

Valid Good Manufacturing Practice (GMP) clearances have been obtained for all proposed manufacturing sites.

Approval is recommended from a pharmaceutical chemistry and quality control aspect.

Nonclinical

Genotoxicity

The potential genotoxicity of molnupiravir and N-hydroxycytidine (NHC) were investigated in the standard battery of tests: a bacterial reverse mutation assay (Ames test), an *in vitro* micronucleus assay (in thymidine kinase 6 (TK6) cells), and the *in vivo* micronucleus assay (in erythrocytes in bone marrow of rats). In addition, *in vivo* mammalian peripheral blood erythrocyte Pig-a mutation assay (in rats) and *in vivo* mutation assay at the cII locus (in Big Blue transgenic F344 rats) were conducted to further investigate mutagenicity in light of positive findings in the bacterial mutation assay. The studies were appropriately designed and conducted.

Molnupiravir and NHC were mutagenic in the bacterial reverse mutation assay (with and without metabolic activation). Molnupiravir was negative in the *in vitro* and *in vivo*

micronuclei tests. Since molnupiravir is efficiently converted to NHC in rat tissues, including the bone marrow, therefore, it was concluded that molnupiravir and NHC were negative for clastogenic activity and/or disruption of the mitotic apparatus *in vivo*. Additional *in vivo* mutagenicity studies (the Pig-a mutagenicity and Big Blue (cII Locus) transgenic rodent assays) were performed in rats with molnupiravir to understand the mutagenicity observed in the bacteria. The tests were conducted per Organisation for Economic Co-operation and Development (OECD) guidelines. Molnupiravir did not produce a clear positive or negative genotoxic effect on red blood cells or circulating reticulocytes in the Pig-a assay (mutation rates observed were within the historical control range (and 95% upper limit) but were at instances higher than concurrent control group) and the assay response was considered equivocal. Molnupiravir did not induce mutation at the cII locus in the liver and bone marrow of male transgenic Fischer 344 Big Blue rats. Based on the all the above, molnupiravir and NHC are considered to be of low risk of genotoxicity in mammalian systems.

Carcinogenicity

No carcinogenicity studies were submitted. This was considered acceptable based on the proposed intended clinical use of < 6 months (short treatment duration in humans, which is limited to 5 days) and low risk of genotoxicity in mammalian systems. Molnupiravir is unlikely to cause cancer from the proposed clinical use.

Reproductive and developmental toxicity

Reproductive and developmental toxicity studies with molnupiravir submitted by the sponsor covered fertility (in rats). These submitted studies were appropriately designed and conducted. All studies involved oral administration.

Embryofetal development (in rats and rabbits) and pre- and post-natal (PPND) development studies were later submitted to the TGA. Further details of these studies have been discussed under 'Additional data submitted by the sponsor' section of this report.

Fertility was unaffected in male rats up to the highest dose tested (500 mg/kg/day: relative exposure, 6). Reductions in mean body weights, body weight gains and food consumption were observed at 500 mg/kg/day. In female rats, there were no molnupiravir related general toxicity effects. No effects were observed on female fertility or early embryonic development up to the highest dose tested (500 mg/kg/day: relative exposure, 2).

In pregnant rats (dosed up to 1000 mg/kg/day from gestation day (GD) 6 to GD17), 2 out of 16 females were euthanised early due to excessive body weight loss (-11.7% and -15.7%) at the highest dose. No treatment related effects on body weight or food consumption were observed at 500 mg/kg/day (relative exposure, 3). Signs of maternal toxicity consisted of reduced body weight gain, body weight loss and transient reduction in food consumption at 1000 mg/kg/day (relative exposure, 7.5). Developmental toxicity at 1000 mg/kg/day included post-implantation loss, reduced fetal growth (reductions in body weight and ossification), fetal malformations (abnormal and/or small or absent eye, small eye socket, absent kidney, detached ribs, vertebra malformations) and variations (cervical ribs and trace supernumerary ribs). Reduced fetal weight and numbers of ossified sacrocaudal vertebrae were observed with treatment at 500 mg/kg/day (relative exposure, 3), which was maternotoxic (reductions in maternal body weight gain and food consumption). The no-observable-effect-level for effects on embryofetal development in the rat is 250 mg/kg/day (relative exposure 0.8). In rabbits (dosed up to 1000 mg/kg/day from GD7 to GD19), reduced fetal weights were observed following treatment at 750 mg/kg/day (relative exposure, 18). Maternotoxicity (reductions in maternal body weight

gain, food consumption and abnormal faecal output) was observed at doses ≥ 400 mg/kg/day (relative exposure 6.5). The no-observable-adverse-effect-level was 125 mg/kg/day for maternal toxicity (relative exposure, 1.5) and 400 mg/kg/day for embryofetal development (relative exposure 6.5). Based on the submitted data, there is a risk of adverse effects on embryofetal development (for example, post-implantation loss, fetal malformations). It is recommended that molnupiravir not be taken by pregnant women.

Clinical

The clinical dossier consisted of the following studies:

- One Phase I study: Study MK-4482-004 (abbreviated as Study 004 hereafter)
- One Phase II study: Study MK-4482-006 (abbreviated as Study 006 hereafter)
- Two Phase II/III studies: Studies MK-4482-001 and MK-4482-002 (abbreviated as Study 001 and Study 002 hereafter)
- One platform trial: Study MK-4482-005 (the AGILE trial; abbreviated as Study 005 thereafter)

Pharmacology

Study 004

Part 1: Single, dose ascending study of 50 to 1600 mg single dose.

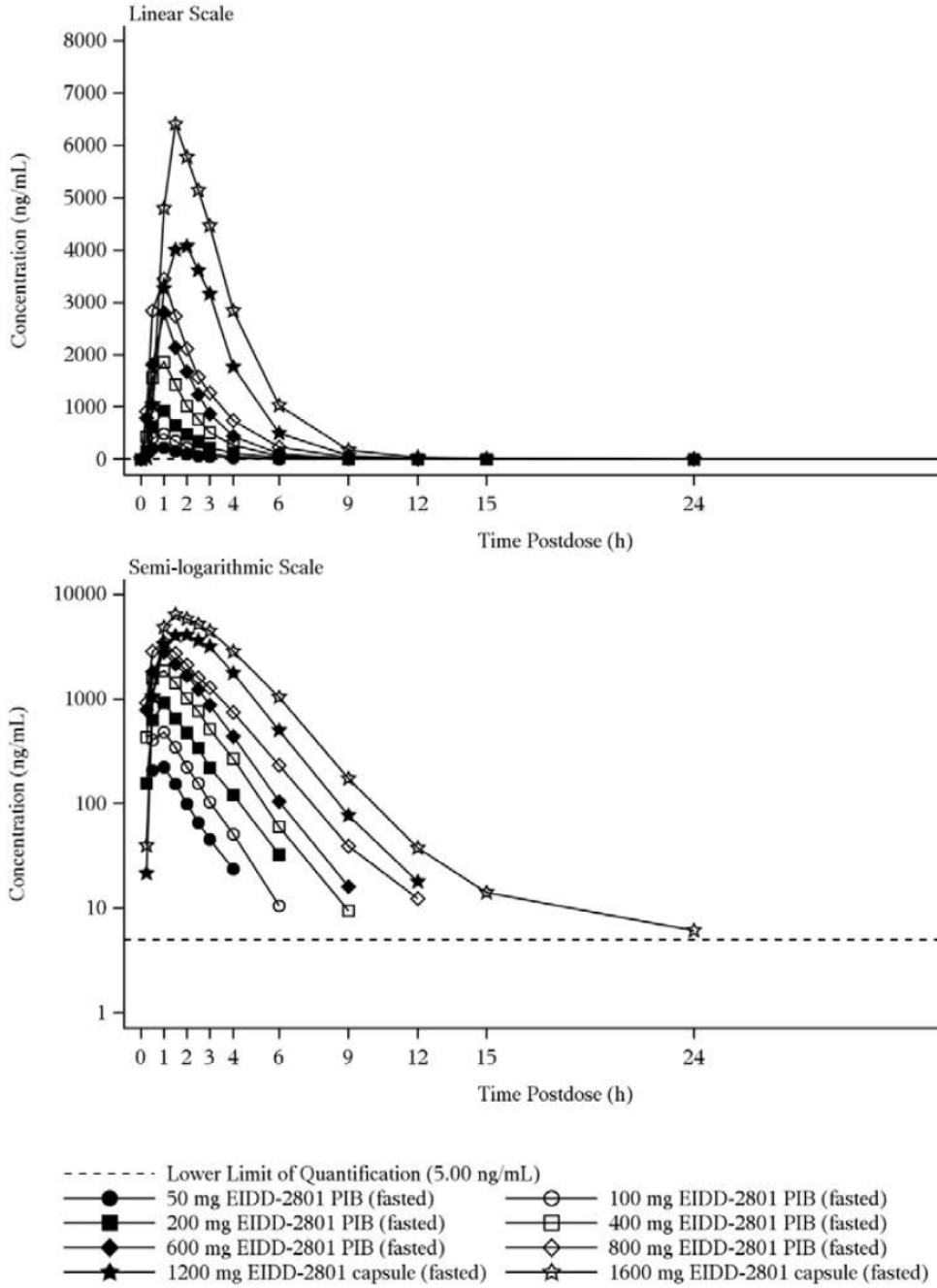
Part 2: food effects study.

Part 3: multiple dose ascending study (50 to 800 mg twice daily for 5 days).

Dose justification

Initially, a maximum starting dose of 200 mg was proposed due to the potential for bone marrow suppressive effects seen in dogs. Subsequently, this was liberalised as there were very few adverse effects observed in humans.

Figure 2: Study EIDD-2801-1001-UK Arithmetic mean plasma concentrations of EIDD-1932 following single oral dose of 50 to 1600 mg molnupiravir



EIDD-2801 = drug development code for molnupiravir; h = hour; PIB = powder in bottle.

The dose proportionality in the 50 to 800 mg range was slightly greater than one for area under the plasma concentration time curve (AUC), and one for maximum concentration (C_{max}). A very small proportion of the drug was excreted in the urine unchanged.

The AUC was similar fed and fasted, the time at maximum concentration (T_{max}) was longer and C_{max} lower in the fed state.

There was no dose accumulation seen in the study evaluating C_{max}, AUC and T_{max} after 5 days.

Pharmacodynamics

Study 006 was a Phase IIb randomised, double blind, placebo controlled trial to evaluate the safety, tolerability and efficacy of molnupiravir to eliminate SARS-CoV-2 viral RNA in patients with COVID-19.

The primary efficacy endpoint was the time to viral RNA negativity. This was determined reverse transcription polymerase chain reaction (RT-PCR) of nasopharyngeal swabs.

Two hundred and two (202) patients were recruited. There was a stepwise progression of dosing from 200 mg twice daily to 800 mg twice daily. Study treatment was to begin within 168 hours (7 days) of symptoms onset.

Viral swabs were analysed by RT-PCR assays, by infectivity assay, and next generation sequencing. The RT-PCR assay utilised in this study was developed based on the United State (US) Centers for Disease Control and Prevention (CDC) 2019-novel coronavirus (nCoV) Emergency Use Authorisation assay. The assay utilises primers specific to the N1 region of the SARS-CoV-2 RNA and has a lower limit of quantification (LLOQ) of 1018 copies/mL.

The infectivity assay utilised in this study is described by Sheahan et al (2020).[32] Briefly, VeroE6 cell monolayers were infected with an aliquot from the sample for one hour. Culture medium was analysed for viral load at 2 and 5 days post-infection by RT-PCR; a positive culture resulted when viral RNA was > 1,000 copies/mL at Day 2 or increased from Day 2 to Day 5 by 0.5 log10 copies/mL. Missing values were imputed by the laboratory if positive cultures were demonstrated at the following time point.

The GenoSure SARS CoV-2 RdRp assay (next generation sequencing assay) was used to amplify and sequence the complete RdRp coding region of the SARS-CoV-2 RNA; minor variants detected at 1% of the viral population were reported. Paired samples from Baseline and Day 5 were sequenced. If the sample on Day 5 was below the LLOQ, then the sample from Day 3 was sequenced.

A total of 202 participants were randomised into the study and received at least one dose of double blind study drug and 195 of those completed the study.

The sponsor has stated that the results show a reduction in viral detection in the molnupiravir 800 mg group. Based on the overall trend of the data, the Delegate suggested that there was a reduction in viral count in each group. The results were statically significant only at Day 5 and 7 for the 800 mg group. There was no dose response. The median time to response was similar for the molnupiravir and placebo groups.

[32] Sheahan, T. P. et al. An Orally Bioavailable Broad-Spectrum Antiviral Inhibits SARS-CoV-2 and Multiple Endemic, Epidemic and Bat Coronavirus, *Sci Transl Med*, 2020; 12 (541): eabb5883.

Table 2: Study EIDD-2801-2003 Summary of key efficacy results

	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	

CI = confidence interval; EOS = end of study; LSM = least squares mean; MMRM = mixed model for repeated measures; N = population size; SARS CoV-2 = severe acute respiratory syndrome coronavirus 2.

Treatment with molnupiravir did not prevent the development of antibodies to SARS-CoV-2. By Day 28 of the study, nearly all participants in all groups had positive antibody status, and more participants in the molnupiravir groups had SARS-CoV-2 antibodies than participants in the placebo group (100.0%, 100.0%, 98.1%, and 96.5% of participants in the molnupiravir 200 mg, 400 mg, and 800 mg, and placebo groups, respectively.

Analysis of the agreement between SARS-CoV-2 RNA and infectivity results indicated a very low level of agreement between the 2 assays. Infectivity results were negative for

every sample that had a negative SARS-CoV-2 RNA result, infectivity results were positive for 45.1% of samples that had a positive SARS-CoV-2 RNA result at Baseline and for 15.6% of all samples that had a positive SARS-CoV-2 RNA result through Day 7 of the study. This would suggest that the virus was not active in many of the samples where the RNA was detected.

Efficacy studies

Table 3: Summary of efficacy studies

Study Number	Title	Dates
001	RCT efficacy, safety and PK study in hospitalised patients with COVID-19	19 October 2020 to 12 February 2021
002	RCT efficacy, safety and PK study in non-hospitalised patients with COVID-19	Part 1 October 2020 to March 2021 Part 2: May 2021 to October 2021 - pivotal study
006 (see above in PD)	A Phase IIa study to evaluate the safety, tolerability and efficacy to eliminate SARS-CoV-2 viral ribonucleic acid detection in persons with COVID-19	19 June 2020 to 21 February 2021
004 (see above PK)	A randomised, double blind, placebo controlled first in human study to evaluate the safety, tolerability and PK of molnupiravir following oral administration in people with COVID-19	10 April 2020 to 24 August 2020

COVID-19 = coronavirus disease 2019; PD = pharmacodynamic(s); PK = pharmacokinetic(s); RCT = randomised controlled trials; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Study 001

Study 001 is a Phase II/III randomised, placebo controlled, double blind clinical study to evaluate the efficacy, safety and pharmacokinetics of molnupiravir in hospitalised adults with COVID-19.

The following report was based upon the interim analysis from Part 1. The study was conducted in 86 centres over 15 countries.

Part 1 was a dose ranging study involving 300 participants:

- Molnupiravir 200 mg twice daily (n = 75)
- Molnupiravir 400 mg twice daily (n = 75)
- Molnupiravir 800 mg twice daily (n = 75)
- Placebo (n = 75)

Dosing was initiated within 10 days after symptom onset and continued for 5 days. Patients were evaluated through to Day 29.

Subjects were included if they were aged 18 years or older, had onset of symptoms and signs of COVID-19 within 10 days before randomisation, were hospitalised, and had mild/moderate or severe COVID-19 (but not critical COVID-19). Exclusion criteria included estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2; human immunodeficiency virus (HIV) with high viral load or low cluster of differentiation 3 (CD3)

cell count; recent chemotherapy; neutrophils less than 500/mm^3; platelets less than 100 000/uL or a stem cell recipient. Participants were not vaccinated.

Three hundred and four (304) patients were randomised. The efficacy analysis was performed on the modified intention-to-treat (mITT)[33] population, which included 293 randomised participants who received at least 1 dose of blinded study intervention.

The mean age was 57.0 years (range 19 to 94 years); 41.4% of the study population was >60 years of age. Most participants (76.3%) received the study intervention > 5 days after symptoms onset. Median time from symptom onset to randomisation was 8.0 days. Baseline COVID-19 severity was moderate or severe for a majority of participants (86.5%). The most common risk factors for severe illness from COVID-19 were age > 60 years (41.4%), obesity (body mass index (BMI) ≥ 30, 40.1%), and diabetes mellitus (23.0%). 87.5% had detectable SARS-CoV-2 RNA in nasopharyngeal sample at Baseline. SARS-CoV-2 baseline nucleocapsid antibody was positive for 31.9% of participants, suggesting previous immunity.

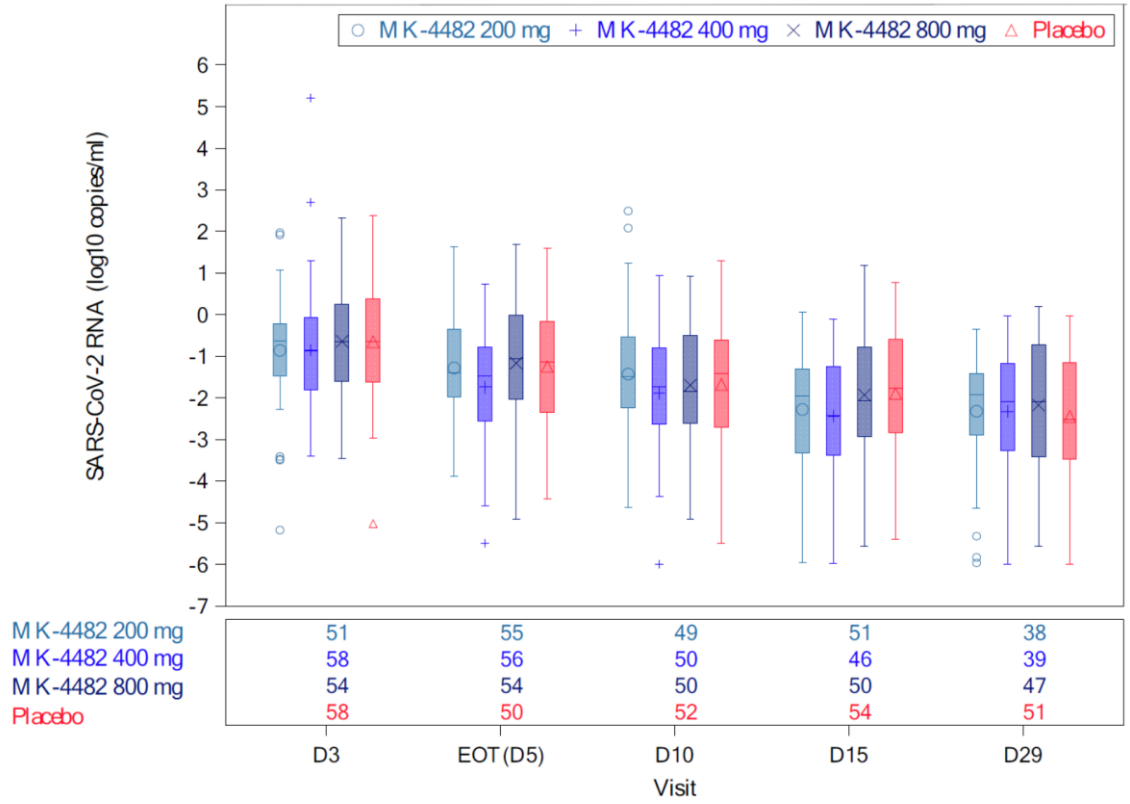
There was no significant treatment effect from intervention with molnupiravir. The rate of sustained recovery was high overall and similar for participants in the molnupiravir groups compared with those in the placebo group. The median time to sustained recovery was 9 days and the recovery rate ranged from 81.5% to 85.2% in each intervention group at Day 29. There were 17 deaths, 15 in the treatment groups and 2 in the placebo group. A similar decrease from Baseline in SARS-CoV-2 RNA mean titre was observed in all groups at all timepoints in nasopharyngeal and oropharyngeal samples (assessed by quantitative polymerase chain reaction (PCR)).

The slope and magnitude of viral load decay were similar across board and with no clear dose-response relationship across molnupiravir groups. No differences in response across molnupiravir doses and placebo for patients with high viral load (> 106 copies/mL) or lower at baseline RNA titres. The post-hoc analyses did not reveal a different result in terms of reduction of viral load over time among the intervention groups.

Proportion of participants with undetectable SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal samples over time, assessed by a quantitative PCR assay, was generally comparable across all groups. Post-hoc analyses by subgroups were consistent with the results in the overall population.

[33] The randomised clinical trials analysed by the **intention-to-treat (ITT)** approach provide unbiased comparisons among the treatment groups. In the ITT population, none of the subjects are excluded, regardless of treatment compliance or attrition due to dropout or crossover, and the subjects are analysed according to the randomisation scheme. A **modified intention-to-treat analysis (mITT)** may sometimes be conducted excluding subjects post-randomisation.

Figure 3: Study MK-4482-001 Interim Analysis 2 Boxplot of mean change from Baseline (log10 copies/mL) in SARS-CoV-2 ribonucleic acid based on quantitation assay nasopharyngeal sample modified intent-to-treat population with baseline SARS-CoV-2 ribonucleic acid titre ≥ 500 copies/mL



D =day; EOT = end of trial; MK-4482 = drug development code for molnupiravir; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

The box represents the interquartile range (IQR) and the horizontal line represents the median. The symbol represents the mean. The whiskers represent the max and min values within 1.5 IQR. Outliers are defined as values from 1.5 IQR to 3 IQR.

The quantitative assay is the second quarter (Q2) SARS-CoV-2 viral load quantitation assay by reverse transcription polymerase chain reaction (RT-PCR).

A higher mutation rate was observed in post-baseline viral sequences from nasopharyngeal swabs in all molnupiravir intervention groups compared with placebo. Additionally, the proportion of participants with > 3 per 10,000 post-baseline sequence mutations (threshold defined post-hoc) from nasopharyngeal swabs was higher in all molnupiravir intervention groups compared with placebo. No trend for increased mutations by molnupiravir dose was observed.

A higher number of adverse events (AEs) resulting in death were reported in the molnupiravir intervention groups compared with the placebo group through Day 15. A total of 16 participants had AEs resulting in death (6 in the molnupiravir 200 mg intervention group, 4 in molnupiravir 400 mg, 4 in molnupiravir 800 mg, and 2 in the placebo group). Most deaths occurred in participants who had severe COVID-19 at Baseline (12/16), were > 60 years of age (13/16), had underlying comorbidities (14/16), and/or had duration of COVID-19 symptoms > 5 days before randomisation (12/16). The investigator did not consider that any deaths were due to the study intervention.

Table 4: Study MK-4482-001 Interim Analysis 2 Participants with adverse events resulting in death during treatment and 14-day follow-up period (incidence > 0% in one or more treatment groups) all participants as treated population

	MK-4482 combined	placebo
Number of patients	218	75
Total number of deaths	14	2
Terms*		
Cardiac arrest	1	0
bacteraemia	1	0
COVID-19	6	0
COVID-19 pneumonia	2	1
Bacterial pneumonia	1	0
Pulmonary sepsis	0	1
Septic shock	1	0
Acute respiratory distress syndrome	1	0
Acute respiratory failure	3	0
Respiratory failure	2	0
shock	1	0

COVID-19 = coronavirus disease 2019; MK-4482 = drug development code for molnupiravir.

* The number of terms is greater than the number of events. Thus, it is likely that some patients had 2 codes.

Study 002

A Phase II/III, randomised, placebo controlled, double blind clinical study to evaluate the efficacy, safety, and pharmacokinetics of molnupiravir in non-hospitalised adults with COVID-19.

Part 1: interim analysis 2

The inclusion criteria included patients 18 years of age or older with laboratory confirms SARS-CoV-2 with a sample collected within 7 days of randomisation. Patients needed to have mild COVID-19 with an underlying condition which puts them at high risk of severe disease, or moderate COVID-19. Patients were excluded if they were currently hospitalised or expected to be hospitalised within 48 hours, had HIV with a viral load of > 50 copies or cluster of differentiation 4 (CD4) < 200 cells/mm^3; chemotherapy within 6 weeks of randomisation, absolute granulocyte count < 500/mm^3; autologous or allogenic hematopoietic stem cell transplant; thrombocytopenia; or history of acute pancreatitis.

The majority of participants were male (52.6%). The mean age was 49.2 years (range 18 to 84 years) with 52% of the participants between 18 to 50 years of age. A majority (66.9%) of participants received study intervention ≤ 5 days after COVID-19 sign/symptom onset and were well balanced for this characteristic across all intervention groups. A majority (75.2%) of participants were at increased risk for severe illness from COVID-19 per medical history. The most common risk factors for developing severe illness were obesity (48.7% BMI ≥ 30), age > 60 years (23.5%), and diabetes mellitus (16.6%).

Participant's COVID-19 severity at Baseline was moderate for 57.0% of participants and mild for 43.0% of participants. SARS-CoV-2 baseline antibody testing was positive for 12.6% of participants. Most participants (81.1%) had detectable SARS-CoV-2.

The number of events across intervention groups were similar. Fewer participants in the molnupiravir groups were hospitalised through Day 29, compared with participants in the placebo group. No participant died and 11 participants were hospitalised through Day 29. One hospitalised participant in the placebo group died on Day 36 (30 days after the last administration of study intervention). All 11 participants who were hospitalised had at least one risk factor for severe illness from COVID-19 including obesity (n = 8), > 60 years of age (n = 5), and diabetes.

Table 5: Study MK-4482-002 Interim Analysis 2 Incidence of death or hospitalisation through Day 29 modified intent-to-treat population

Treatment	N	n (%)	Treatment vs. Placebo		
			Unadjusted Difference	Adjusted Difference in Rates % (95% CI)[a]	p-Value
MK-4482 200 mg	74	1 (1.4)	-4.1	-4.1 (-12.2, 2.5)	0.1676
MK-4482 400 mg	77	3 (3.9)	-1.5	-1.5 (-9.9, 6.2)	0.6668
MK-4482 800 mg	74	3 (4.1)	-1.4	-1.3 (-9.6, 6.4)	0.7141
Placebo	74	4 (5.4)			

CI = confidence interval; MK-4482 = drug development code for molnupiravir; N = population size; n = sample size; vs. = versus.

a Adjusted differences, the corresponding confidence intervals and p-values are based on Miettinen and Nurminen method stratified by randomisation strata.

Unknown Day 29 survival status is treated as failure.

Post-hoc subgroup analyses of the primary endpoint for participants > 60 years of age, time from COVID-19 symptom onset ≤ 5 days prior to the day of randomisation, and those at increased risk for severe illness from COVID-19, suggested that participants who received molnupiravir (any dose) generally exhibited improved outcomes compared with participants who received placebo. However, the study was not powered to detect whether or not these results were statistically significant. No trends by molnupiravir dose were observed.

Table 6: Study MK-4482-002 Interim Analysis 2 Incidence of death or hospitalisation through Day 29 modified intent-to-treat population participants at increased risk of severe illness from COVID-19

Treatment	N	n (%)	Treatment vs. Placebo	
			Difference in Rates % (95% CI)[a]	p-Value
MK-4482 200 mg	56	1 (1.8)	-5.6 (-16.1, 3.0)	0.1589
MK-4482 400 mg	60	3 (5.0)	-2.4 (-13.3, 7.5)	0.5945
MK-4482 800 mg	54	3 (5.6)	-1.9 (-12.9, 8.8)	0.6973
Placebo	54	4 (7.4)		

CI = confidence interval; MK-4482 = drug development code for molnupiravir; N = population size; n = sample size; vs. = versus.

a Differences, the corresponding confidence intervals and p-values are based on Miettinen and Nurminen method.

Table 7: Study MK-4482-002 Interim Analysis 2 Incidence of death or hospitalisation through Day 29 modified intent-to-treat population participants with time from symptom onset prior to randomisation ≤ 5 days

			Treatment vs. Placebo	
Treatment	N	n (%)	Difference in Rates % (95% CI)[a]	p-Value
MK-4482 200 mg	51	1 (2.0)	-6.0 (-17.2, 3.3)	0.1639
MK-4482 400 mg	52	2 (3.8)	-4.2 (-15.6, 6.2)	0.3751
MK-4482 800 mg	48	1 (2.1)	-5.9 (-17.1, 3.9)	0.1855
Placebo	50	4 (8.0)		

CI = confidence interval; MK-4482 = drug development code for molnupiravir; N = population size; n = sample size; vs. = versus.

a Differences, the corresponding confidence intervals and p-values are based on Miettinen and Nurminen method.

An additional post-hoc analysis indicated a generally lower rate of hospitalisation for molnupiravir versus placebo in participants who had started study intervention early (that is, ≤ 5 days after symptom onset) and were also at increased risk of severe illness from COVID-19; 4/107 (3.7%) participants were hospitalised in the combined molnupiravir intervention groups compared with 4/34 (11.8%) participants in the placebo group.

Table 8: Study MK-4482-002 Interim Analysis 2 Incidence of death or hospitalisation through Day 29 modified intent-to-treat population participants with time from symptom onset prior to randomisation ≤ 5 Days and at increased risk of severe illness from COVID-19

			Treatment vs. Placebo	
Treatment	N	n (%)	Difference in Rates % (95% CI)[a]	p-Value
MK-4482 200 mg	38	1 (2.6)	-9.1 (-24.5, 3.5)	0.1307
MK-4482 400 mg	38	2 (5.3)	-6.5 (-22.3, 7.5)	0.3224
MK-4482 800 mg	31	1 (3.2)	-8.5 (-24.1, 6.1)	0.2004
Placebo	34	4 (11.8)		

CI = confidence interval; MK-4482 = drug development code for molnupiravir; N = population size; n = sample size; vs. = versus.

a Differences, the corresponding confidence intervals and p-values are based on Miettinen and Nurminen method.

Time to sustained resolution or improvement and time to progression of each targeted self-reported COVID-19 sign/symptom was similar across groups. The severity of each of the 15 self reported clinical signs and symptoms of COVID-19 generally improved for the majority of participants across intervention groups from Day 1 through Day 29, as shown in the decreased proportion of participants overtime reporting 'moderate' or 'severe' for these symptoms.

The observed median time to sustained improvement or resolution was ≤ 12 days for all symptoms. The sustained resolution or improvement rate was generally comparable for all intervention groups through Day 29.

A comparable decrease in mean SARS-CoV-2 RNA titre relative to Baseline in nasopharyngeal and oropharyngeal samples, as assessed by quantitative RT-PCR, was observed in all intervention groups at all timepoints.

Post-hoc subgroup analysis of participants with time from symptom onset prior to randomisation ≤ 5 days showed a greater reduction in the mean change from Baseline in SARS-CoV-2 viral RNA titre (log RNA copies/mL), -3.39 logs in the 800 mg molnupiravir group compared with -2.61 logs in the placebo group at end of trial of Day 5.

For participants with detectable SARS-CoV-2 RNA in nasopharyngeal samples at Baseline, a higher proportion of participants in the 400 mg and 800 mg groups had undetectable RNA results compared with placebo at Days 5 (end of trial), 10, 15, and 29. These results are a little different to what was observed in Study 006. Results for the 200 mg molnupiravir group were generally comparable to placebo at all timepoints.

Higher viral sequence mutation rates (per 10,000 bp) were observed at Day 5 in nasopharyngeal samples obtained from participants treated with molnupiravir 200 mg (7.9), molnupiravir 400 mg (6.7) and molnupiravir 800 mg (8.7) compared with placebo (2.0). The highest RNA mutation rate was observed in the molnupiravir 800 mg intervention group at Day 5.

SARS-CoV-2 mutations observed post-Baseline were distributed across the entire 30,000 bp genome with no increase of treatment emergent mutations in the RdRp active site. The increase in mutation rate was not observed in matched oropharyngeal swab sample

Part 2: interim analysis 4 (pivotal study)

The Phase III part of Study 002 was initiated in May 2021. Participants were enrolled 1:1 to receive molnupiravir 800 mg or placebo every 12 hours for 5 days and followed for the primary efficacy evaluation for through Day 29. Inclusion criteria included mild to moderate symptoms with one or more than one risk factor for severe disease. Randomisation was stratified by time to symptom onset (< 3 days or > 3 days). Interim analysis 4 was planned when 50% were followed to Day 29.

All randomised participants reported symptom onset within 5 days prior to randomisation with approximately half of the participants having symptom onset ≤ 3 days prior to randomisation.

All participants had more than one risk factor for severe COVID-19.

Table 9: Study MK-4482-002 Combined Interim Analysis 3 and 4 Risk factors for severe illness from COVID-19 all randomised participants

Risk Factors for Severe Illness from COVID-19						
At least one risk factor	385	(99.5)	384	(99.0)	769	(99.2)
Age >60 years	51	(13.2)	55	(14.2)	106	(13.7)
Active Cancer	6	(1.6)	11	(2.8)	17	(2.2)
Chronic Kidney Disease	14	(3.6)	20	(5.2)	34	(4.4)
Chronic Obstructive Pulmonary Disease	7	(1.8)	22	(5.7)	29	(3.7)
Obesity (BMI ≥ 30)	306	(79.1)	287	(74.0)	593	(76.5)
Serious Heart Condition	42	(10.9)	36	(9.3)	78	(10.1)
Diabetes Mellitus	48	(12.4)	57	(14.7)	105	(13.5)

BMI = body mass index; COVID-19 = coronavirus disease 2019.

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).

85.5% of participants had detectable SARS-CoV-2 RNA (nasopharyngeal sample) and 18.2% of participants had positive SARS-CoV-2 antibody results (via Roche Elecsys anti-SARSCoV-2 total nucleocapsid antibody assay) at Baseline.

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 variant, 35.0%), 21A (delta variant, 22.4%), and 20J (gamma variant, 22.4%).

The primary efficacy endpoint was hospitalisation or death through to Day 29 (primary endpoint). There were fewer participants that were hospitalised or died in the molnupiravir group, 28 (7.3%) than the placebo group, 53 (14.1%). Treatment with

molnupiravir 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.

Table 10: Study MK-4482-002 Combined Interim Analysis 3 and 4 Summary of hospitalisation or death through Day 29 modified intent-to-treat population

	MK-4482 800 mg		Placebo	
	n	(%)	n	(%)
Participants in population	385		377	
Hospitalization or Death	28	(7.3)	53	(14.1)
Hospitalization	28	(7.3)	52	(13.8)
Death	0	(0.0)	8	(2.1)
Unknown Day 29 Survival Statusa	0	(0.0)	1	(0.3)

MK-4482 = drug development code for molnupiravir; n = sample size.

n= number of participants with the corresponding event.

Every participant is counted a single time for each applicable row and column. Participants who died were hospitalised prior to death; such participants are counted once each in the hospitalisation and death rows.

a Unknown survival status at Day 29 was counted as having an outcome of hospitalisation or death in the primary efficacy analysis.

In the subgroup of participants positive for SARS-CoV-2 nucleocapsid antibodies at Baseline (suggesting recent or prior SARS-CoV-2 infection). There was no difference between intervention groups in the percentage of participants who were hospitalised or died in this subgroup.

Table 11: Study MK-4482-002 Combined Interim Analysis 3 and 4 Incidence of Hospitalisation or death through Day 29 by SARS-CoV-2 baseline antibody modified intent-to-treat population

	MK-4482 800 mg		Placebo		Difference	
	n/m	(%)	n/m	(%)	%	(95% CI)[a]
Participants in population	385		377			
SARS-CoV-2 Baseline Antibody						
Positive	2/70	(2.9)	2/69	(2.9)	-0.0	(-7.5, 7.3)
Negative	23/299	(7.7)	49/287	(17.1)	-9.4	(-14.9, -4.1)

m= number of participants in the modified intent-to-treat population with the corresponding group; MK-4482 = drug development code for molnupiravir; n = number of participants died or hospitalised through Day 29; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

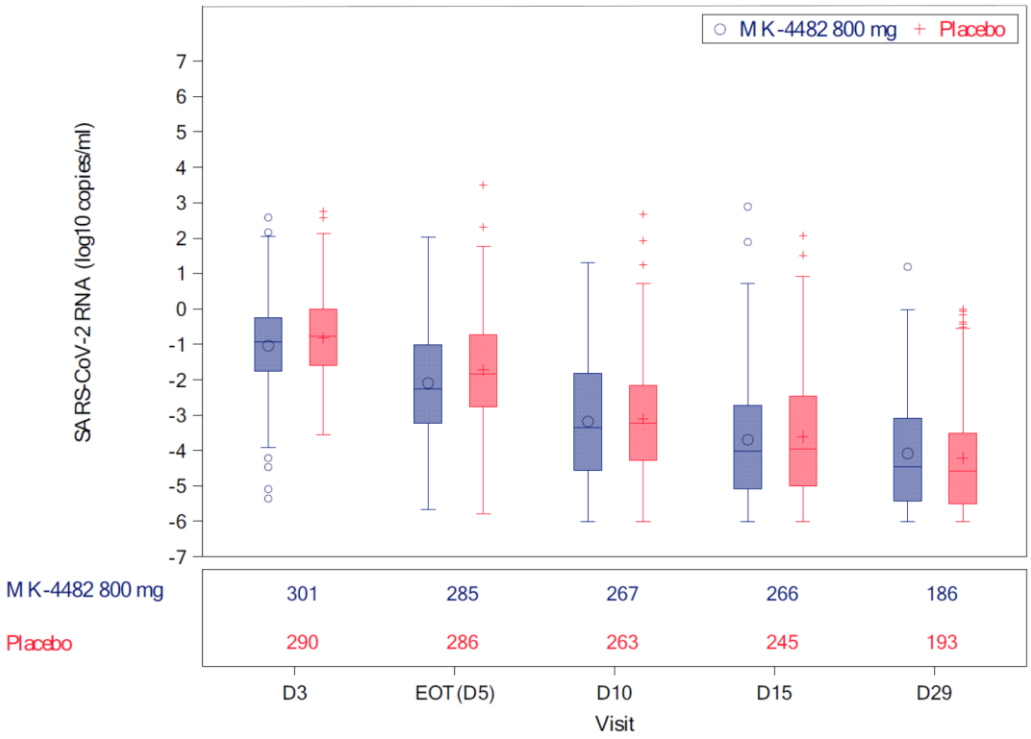
a The corresponding confidence interval is based on Miettinen and Nurminen method.

Unknown survival status at Day 29 was counted as having an outcome of hospitalisation or death.

There was minimal impact on symptoms.

After adjusting for baseline RNA titre, mean SARS-CoV-2 viral RNA titres were lower at Days 3 and 5 in the molnupiravir group compared with the placebo group. The adjusted mean difference in SARS-CoV-2 RNA (in log10 scale; molnupiravir 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 titre for the molnupiravir group compared with the placebo group, respectively. The reduction in RNA titre was not significant at other time points.

Figure 4: Study MK-4482-002 Combined Interim Analysis 3 and 4 Boxplot of mean change from Baseline (log10 copies/mL) in SARS-CoV-2 ribonucleic acid based on quantitation assay nasopharyngeal sample modified intent-to-treat population



D =day; EOT = end of trial; MK-4482 = drug development code for molnupiravir; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

The box represents the interquartile range (IQR) and the horizontal line represents the median. The symbol represents the mean.

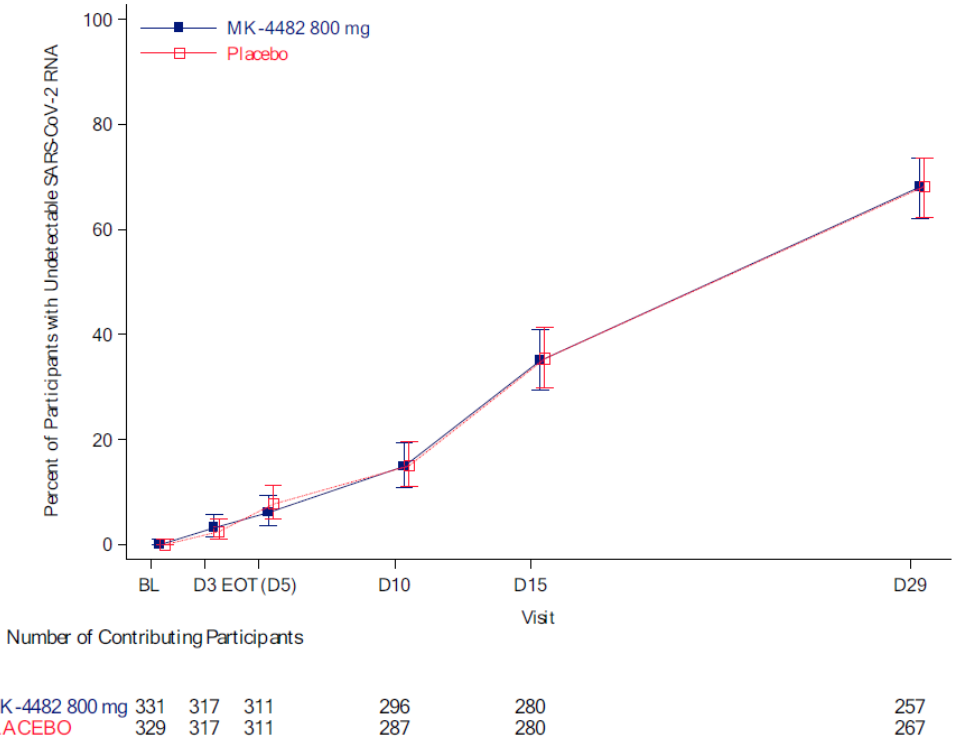
The whiskers represent the max and min values within 1.5 IQR. Outliers are defined as values from 1.5 IQR to 3 IQR.

The quantitative assay is the second quarter (Q2) SARS-CoV-2 Viral load quantitation assay by reverse transcription polymerase chain reaction (RT-PCR).

Analysis only includes participants with baseline SARS-CoV-2 RNA titre ≥ 500 copies/mL.

The percentage of participants who achieved undetectable SARS-CoV-2 RNA in nasopharyngeal 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 titre.

Figure 5: Study MK-4482-002 Combined Interim Analysis 3 and 4 Proportion of participants with undetectable SARS-CoV-2 ribonucleic acid over time based on qualitative assay nasopharyngeal sample modified intent-to-treat population



D =day; EOT = end of trial; MK-4482 = drug development code for molnupiravir; RNA = ribonucleic acid; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

The qualitative assay is the Roche Cobas SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR).

Analysis only includes participants with detectable SARS-CoV-2 RNA at Baseline.

Safety

Exposure

Approximately 600 patients have been exposed to the proposed dose in clinical studies as of Study 002 Interim Analysis 4.

Table 12: Numbers of participants exposed to the proposed dose in clinical studies

Study		Number of Participants										Dosing Regimen	Duration of Rx (day)
		Molnupiravir Dose (mg)											
		50	100	200	300	400	600	800	1200	1600	Total		
Study P004 (Ph1)	Part 1	6	6	6	0	6	6	6	6	6	48	single dose	
	Part 2	0	0	10	0	0	0	0	0	0	10	single dose	
	Part 3	6	6	6	6	6	6	6	0	0	42	Q12H	5.5
P006 (Ph2a)		0	0	23	0	62	0	55	0	0	140	Q12H	5
P001 (Ph2)	Part 1	0	0	73	0	73	0	72	0	0	218	Q12H	5
P002 (Ph2/3)	Part 1	0	0	74	0	77	0	74	0	0	225	Q12H	5
	Part 2	0	0	0	0	0	0	386	0	0	386	Q12H	5
Total		12	12	192	6	224	12	599	6	6	**1069**		

Ph = phase; Rx = reaction.

Study 002 Part 2 (Interim Analysis 4)

A total of 765 non-hospitalised participants with COVID-19 received at least one dose of study intervention and were included in the study population (386 participants in the molnupiravir 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 percentage of participants with at least one AE was comparable between the molnupiravir and placebo groups (35.0% and 39.6% participants, respectively). The observed percentages of participants with serious adverse events (SAEs), SAEs leading to discontinuation of study intervention, and AEs leading to death were lower in the molnupiravir group compared with the placebo group. The most frequently reported AEs (≥ 5% of participants in either group) were COVID-19 (molnupiravir 8.0%, placebo 14.8%) and COVID-19 pneumonia (molnupiravir 4.9%, placebo 9.0%).

No participant in the molnupiravir group had laboratory values that met the predefined event of clinical interest (ECI) criteria for potential drug induced liver injury (DILI)[34] or for platelet count of < 50,000 cells/μL). No evidence of hematologic toxicity was observed in participants who received molnupiravir. Participants aged ≥ 65 years had higher rates of SAEs compared with participants aged < 65 years in both intervention groups.

Study 002 Part 1

The incidence and type of AEs were comparable across the intervention groups.

The most frequently reported (≥ 5% in any group) AEs during the treatment period through the 14-day follow-up were COVID-19 pneumonia (5.4%) in the molnupiravir 800 group and diarrhea (5.4%) and COVID-19 (6.8%) both in the placebo group.

Study 001

Overall, AEs were reported for 57.0% of participants. AEs considered related to study intervention were reported for 13.7% of participants. SAEs were reported for 15.4% of participants; one SAE was considered to be related to study intervention. There were 16 deaths, the number of deaths was higher in the molnupiravir group than the placebo group.

The incidence and type of most frequently reported AEs were comparable across groups.

- The most frequently reported AEs (> 5%) in any of the molnupiravir intervention groups were COVID-19, aspartate transaminase (AST)/alanine transaminase (ALT) elevations, constipation, bacterial pneumonia, hyperglycaemia, and respiratory failure.
- The most frequently reported AEs (> 5%) in the placebo group were constipation, COVID-19, COVID-19 pneumonia, ALT increased, and respiratory failure.
- No trends by molnupiravir dose or risk differences by intervention group were observed.

[34] **Drug induced liver injury (DILI)** also known as drug-induced hepatoxicity, is acute or chronic liver damage caused by a prescription, over the counter (OTC) or complementary medicine. Hepatoxicity due to type A reactions, or intrinsic DILI is typically dose-related and occurs in a large proportion of individuals exposed to the drug, (predictable) and onset is within a short time span (hours to days). Idiosyncratic DILI is not closely dose-related, and occurs in only a small proportion of exposed susceptible individuals (unpredictable) and exhibits a variable latency to onset of days to weeks.

Table 13: Study MK-4482-002 Part 2 Expected future data

Expected future data		
Study MK-4482-002 Part 2	Following the data base for the Interim Analysis 3/4 analysis, an additional 658 participants were enrolled	Top line efficacy and safety data through to Day 29 for all 1433 enrolled subjects will be available by the end of 2021 The final study report will be available at the first quarter of 2022 The late follow up 7 months after dosing will be available at the second quarter of 2022;[35]

Risk management plan

The sponsor has submitted EU-risk management plan (RMP) version 0.1 (dated 14 October 2021; data lock point (DLP) 18 September 2021) and Australia specific annex (ASA) version 0.1 (dated 28 October 2021) in support of this application. The sponsor has submitted an updated ASA version 0.2 (dated 14 December 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 14.[36]

Table 14: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	None	–	–	–	–
Missing information	Safety in pregnancy	✓[1]	–	✓	–
	Safety in lactation	✓	–	✓	–

[1] Pregnancy follow-up questionnaire

[35] The sponsor requested amendment: the 7-month safety data for MOVe-OUT is expected to be available in approximately the fourth quarter of 2022.

[36] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the Product Information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- The list of 'summary of safety concerns' is inadequate in showing the important safety concerns. In addition to the risks listed above, the important potential risks should include: embryofoetal toxicity and teratogenicity, bone marrow toxicity. Safety in immunocompromised patients needs to be further characterised to support the use in this group.
- The sponsor should propose additional pharmacovigilance activity with Australian patients included to monitor safety during pregnancy. Safety findings from the additional pharmacovigilance activity should be reported annually in the periodic safety update reports (PSURs).
- The RMP evaluator has made recommendations to the TGA delegate to improve patient selection and risk communication.

Risk-benefit analysis

Delegate's considerations

The sponsor has submitted an application for the provisional registration of molnupiravir for the treatment of COVID 19. The submission was assessed as part of a workshare arrangement.

The quality evaluator recommended approval. There are no concerns preventing registration.

The nonclinical data identified potential concerns about bone marrow toxicity in dogs, these have not been seen in the clinical studies. There were concerns about bone dysplasia in a juvenile animal model. This finding was not considered relevant for adults. Further data will be available before the sponsor submits an application for use in children. There are potential concerns about use in pregnancy.

The pivotal clinical data (Study 002 Part 2) in support of the application was a Phase III study in non-hospitalised patients with mild-moderate COVID-19 with risk factors for severe disease. These included obesity, diabetes, COPD. This group was chosen as a Phase II study in non-hospitalised adults showed greater benefits in this subgroup. This study showed an absolute risk reduction of around 6%, relative risk reduction of 50%, in the risk of hospitalisation or death. Another Phase II study performed in hospitalised adults with COVID-19 (and who commenced treatment later) failed to show an improvement in time to recovery. In fact, there was a higher rate of death in those treated with molnupiravir than the placebo group. Early data suggested that giving molnupiravir early in the course of disease may result in improved outcomes. However, the results of the Phase III study did not show a significant difference in endpoints between those who commenced the medication more or less than 3 days after symptom onset.

There was a minimal change in symptom scores with treatment in any study.

All subjects in the study were unvaccinated. There was no significant improvement in hospitalisation or death in patients with positive nucleocapsid antibodies at Baseline.

The clinical studies showed a reduction in viral load that was similar in both the molnupiravir and placebo groups over the 29 day follow up period. In Study 002 Part 2 there was reduction in viral load in the 800 mg group on Days 3 to 5, but not at later times. The sponsor has stated that there was undetectable viral RNA in the treatment groups by Day 30, however this was also true for the placebo group. In his report, the expert advisor discusses the variability in viral titres from oral and nasal swabs due to factors related to collection. The other consideration is whether the virus detected by PCR is active or not. In Study 006, the sponsor also used an infectivity assay. This showed a reduction (but not elimination) of infectivity in the molnupiravir group.

Overall, molnupiravir was well tolerated with similar number of AEs between the treatment and placebo groups. The main AEs detected were pneumonia, diarrhoea and mild elevation of transaminases. However, the safety data is limited to < 1000 subjects followed for 30 days.

Impact of increased viral mutation rate on swabs

There was an increase rate of RNA mutation detected in the swabs taken. The sponsor has stated that based on the mechanism of action of error induction, it is exceedingly unlikely that molnupiravir treatment will lead to new variants of SARS-CoV-2. The error burden introduced with treatment by molnupiravir leads to high numbers of mutations in the viral genome, most of which are likely to be detrimental to the ability of virus to replicate (that is, introduction of missense errors, stop codons, or altering viral RNA secondary structure). In addition, in cell culture selection experiments with viruses other than coronaviruses, there has not been any evidence that NHC treatment leads to emergence of a new virus variants with enhanced fitness. The majority of sequence changes observed were transition errors and were distributed randomly across the viral RNA genome at very low frequency.

Potential impact of pregnancy and the fetus

Currently available data that inform on embryofetal toxicity are as follows. In pregnant rats administered molnupiravir during the organogenesis period, embryofetal lethality and teratogenicity were observed at 1000 mg/kg/day (8-fold the NHC clinical area under the plasma concentration time curve from time zero to 24 hour ($AUC_{0\text{-}24hr}$) exposure at the recommended human dose (RHD)). Similar findings were not seen in rats at 500 mg/kg/day (3-fold the NHC clinical $AUC_{0\text{-}24hr}$ exposure at the RHD); embryofetal developmental findings at 500 mg/kg/day were limited to reduced fetal growth. There was no embryofetal lethality or teratogenicity observed in pregnant rabbits dosed during the organogenesis period up to 750 mg/kg/day (18-fold the NHC clinical $AUC_{0\text{-}24hr}$ exposure at the RHD). In addition, preliminary results from the pre- and post-natal development study (PPND) in which female rats were administered molnupiravir from gestation Day 6 through lactation Day 20 up to the maximum tolerated dose, 500 mg/kg/day (2-fold the NHC clinical $AUC_{0\text{-}24hr}$ exposure at the RHD), did not demonstrate effects on development, growth, reproductive performance, or fertility of the offspring.

Based on the embryofetal lethality and teratogenicity only in the rat study at 8-fold the clinical NHC exposure, the sponsor's position is that molnupiravir is not recommended in pregnancy and that women of childbearing potential use reliable contraception for the duration of systemic NHC exposure (during treatment and for 4 days after the last dose).

Contraception in men is not required given that there was one) no evidence of *in vivo* genotoxicity or mutagenicity 2) no male reproductive findings of concern in general toxicity or male fertility studies 3) low risk of embryofetal harm in a women of childbearing potential through exposure to the ejaculate of a male partner exposed to molnupiravir, given the extremely low estimated NHC exposure through exposure to semen compared to NHC exposure achieved at the no-observed effect level in animal reproduction studies. The NHC exposure at the no-observed effect level in the embryofetal developmental toxicity study in rats was similar to (0.8-fold) the clinical exposure at the RHD, and > 1000 fold higher than the estimated NHC concentration in the female's blood after exposure to the drug in semen.

The UK and MHRA Product Information states that women of childbearing potential must use an effective form or contraception but have not recommended a negative pregnancy test before treatment.

Potential impact on cancer

In this review, the expert advisor mentioned concerns about the potential for mammalian cell mutagenesis. This is because NHC acts as mutagen in other polymerases and it has been shown *in vitro* on hypoxanthine phosphorybosyl transferase gene knockout assays to be mutagenic to hamster (Chinese hamster ovary (CHO)-k1) cells. This is of significant concern as:

- the mechanism of action of molnupiravir involves insertion of the mutated base into the sequence,
- there have been no long-term human studies.

However, the nonclinical evaluator was satisfied with the genotoxicity and carcinogenicity data submitted.

Proposed action

At this time, the Delegate would recommend approval of molnupiravir in the following restricted population: adults with confirmed COVID-19 within 5 days of symptom onset with risk factors for severe disease but do not currently require oxygen.

The Delegate is uncertain about the use of molnupiravir in vaccinated subjects with COVID-19. Although it is likely to reduce viral load in a similar way to that seen in unvaccinated, the relative benefits in terms of reduction in hospitalisation are unknown.

The reasons for my decision are as follows:

- efficacy for the primary endpoint was demonstrated in this group;
- there are significant unknown safety concerns due to low subject numbers, short duration of follow up, preclinical concerns about use in pregnancy. In addition this is a novel drug with no previous history of use;
- there is the potential for very widespread use without this restricted indication;
- Australia is fortunate to have very high vaccination rates and low patients numbers at the moment. There are other medications available for the treatment of patients with COVID-19 in patients with mild-moderate disease;
- although the risk of this medication causing a variant of concern is thought to be unlikely, the risk is unknown.

These restrictions could be reconsidered when further information is received about efficacy and safety in populations not previously studied,

Questions for the sponsor

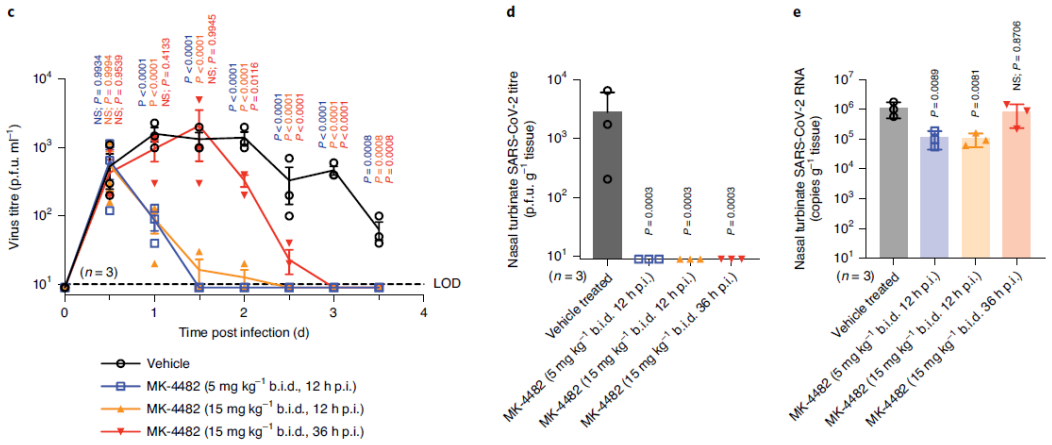
The sponsor provided the following response to questions from the Delegate.

1. ***When reading the nonclinical report, the Delegate got the impression that there was a greater reduction in viral loads in the animal studies than in the human studies. Please comment.***

As noted, molnupiravir (MOV, MK-4482/EIDD-2801) has been evaluated in several animal models of SARS-CoV-2 infection including ferret, hamster and mouse models. In most animal studies molnupiravir did not show large reductions in viral RNA but showed a

profound impact on the production of infectious virus.[37,38,39] As shown in Figure 6 (adapted from Cox et al. 2021);[37] treatment with molnupiravir, significantly decreased infectious titre in nasal lavage (panel c) and nasal turbinates (panel d) by greater than 2 logs by Day 4 post-infection. However, reductions in viral RNA levels in the nasal turbinates was less pronounced, with only about a one log reduction in RNA titre in animals treated 12 hours post-infection (panel e) and only modest reductions in animals treated 36 hours post-infection. Despite the smaller changes in RNA levels, no infectious virus was recovered from nasal turbinates by Day 4 post-infection (panel d).

Figure 6: Therapeutic molnupiravir is orally efficacious against SARS-CoV-2 in ferrets (figure adapted from Cox et al. 2021)[37]



b.i.d. = twice daily; d = day(s); EIDD-2801 = drug development code for molnupiravir; h= hour; MK-4482 = drug development code for molnupiravir; n= sample size; NS = not significant; p.f.u. = plaque forming unit; p.i. = post-infection; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

c. Viral titres of the nasal lavages of the infected ferrets. Treatment with MK-4482/EIDD-2801 significantly reduced the virus titres within 12 hour of dosing onset in all treatment groups. Statistical analysis was performed using a two-way analysis of variance (ANOVA) with Dunnett's multiple comparison post-hoc test.

d and e. Infectious particle;

d. and viral ribonucleic acid (RNA) copy;

e. numbers in the nasal turbinates of infected ferrets extracted 4 days after infection. Statistical analysis was performed using a one-way ANOVA with Dunnett's multiple comparison post-hoc test.

c to e. p-values are shown.

The number of independent biological repeats is shown for each panel; symbols represent independent biological repeats (individual animals); lines connect the group mean ± standard deviation (s.d.) (a,c) and bar graphs show the mean ± s.d. (d,e).

Consistent with the observations in animal models, data from the sponsor's clinical trial (Study 002 Part1) showed greater reduction in viral RNA titres from nasopharyngeal samples in molnupiravir participants compared with placebo at early timepoints in participants treated within 5 days of symptom onset, although the differences were of lower magnitude (< 1 log) compared with RNA reductions in the animal studies. However, similar to the animal studies, infectivity data from clinical trials, Studies 006, 001 (Part 1)

[37] Cox, R. M. et al. Therapeutically Administered Ribonucleoside Analogue MK-4482/EIDD-2801 Blocks SARS-CoV-2 Transmission in Ferrets, *Nat Microbiol*, 2021; 6 (1): 11–18
[38] Sheahan, T. P. et al. An Orally Bioavailable Broad-Spectrum Antiviral Inhibits SARS-CoV-2 in Human Airway Epithelial Cell Cultures and Multiple Coronaviruses in Mice, *Sci Transl Med*, 2020; eabb5883.
[39] Rosenke, K. et al. Orally Delivered MK-4482 Inhibits SARS-CoV-2 Replication in the Syrian Hamster Model, *Res Sq*, 2020; rs.3.rs-86289.

and 002 (Part 1), showed that no infectious virus was recoverable from any participant receiving 800 mg of molnupiravir by study Day 5 (Table 15 and Table 16). Together, both the animal and human studies demonstrate that molnupiravir has potent antiviral activity that quickly renders the SARS-CoV-2 non-infectious.

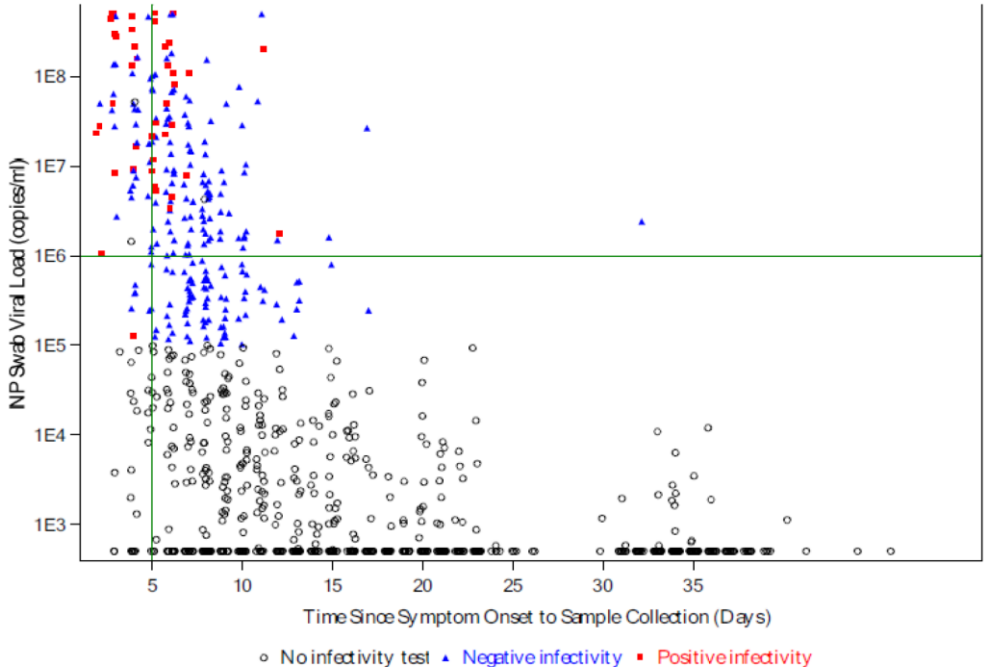
2. Was an infectivity analysis performed in any study other than Study 006?

Infectivity analyses are available from the Phase II portion (Parts 1) of the Phase II/III placebo controlled trials evaluating molnupiravir in hospitalised (Protocol 001 (Study 001)) and non-hospitalised (Protocol 002 (Study 002)) patients.

3. Is it possible to break down the PCR or viral load results to show how many of those with had positive PCR virus detected also have a positive infectivity results, in particular the difference before and after treatment?

In Part 1 of both Studies 001 and 002, viral infectivity was measured by plaque assay in Vero cell cultures for nasopharyngeal and oropharyngeal samples with viral RNA titres ≥ 100,000 copies/mL. Samples with viral RNA below 100,000 copies/mL were not evaluated and imputed as negative. In general, infectious virus was only recovered in samples with RNA titres above 106 RNA copies/mL and collected within approximately 7 days of symptom onset (Study 002, Part 1, Figure 7, all dose groups). The proportion of subjects with undetectable infectivity results at Baseline and Study Days 3, 5, 10, 15 and 29 are shown in Table 15. Overall, the proportion of participants with positive infectivity at Baseline was low, however, by study Day 5 100% of molnupiravir participants had negative infectivity compared with 66/69 (95.7%) placebo participants. Similar results were observed in nasopharyngeal samples from Study 001, Part 1 (Table 16).

Figure 7: Study MK-4482-002 Part 1 Plot of SARS-CoV-2 infectivity by viral ribonucleic acid titre and time since symptom onset nasopharyngeal sample modified intent-to-treat population with negative baseline antibody



NP = nasopharyngeal; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

SARS-CoV-2 viral ribonucleic acid (RNA) titre was determined using a quantitative reverse transcription polymerase chain reaction (RT-PCR) assay developed at Q2 solutions, Morrisville, NC, USA.

Samples with viral RNA titre below 100,000 copies/mL were not evaluated for infectivity.

SARS-CoV-2 infectivity was determined by plaque assay in Vero cell culture (LabCorp Inc, Indianapolis, IN, USA.

Table 15: Study MK-4482-002 Part 1 Proportion of participants with undetectable SARS-CoV-2 infectivity titres over time nasopharyngeal sample modified intent-to-treat population

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Baseline	61/70	87.1 (77.0, 93.9)	61/76	80.3 (69.5, 88.5)	56/68	82.4 (71.2, 90.5)	62/70	88.6 (78.7, 94.9)
Day 3	67/68	98.5 (92.1, 100.0)	72/74	97.3 (90.6, 99.7)	64/66	97.0 (89.5, 99.6)	67/68	98.5 (92.1, 100.0)
EOT (Day 5)	68/68	100.0 (94.7, 100.0)	72/72	100.0 (95.0, 100.0)	63/63	100.0 (94.3, 100.0)	66/69	95.7 (87.8, 99.1)
Day 10	65/65	100.0 (94.5, 100.0)	71/71	100.0 (94.9, 100.0)	57/57	100.0 (93.7, 100.0)	61/62	98.4 (91.3, 100.0)
Day 15	66/66	100.0 (94.6, 100.0)	69/69	100.0 (94.8, 100.0)	65/65	100.0 (94.5, 100.0)	62/62	100.0 (94.2, 100.0)
Day 29	62/62	100.0 (94.2, 100.0)	68/68	100.0 (94.7, 100.0)	58/58	100.0 (93.8, 100.0)	64/64	100.0 (94.4, 100.0)

CI = confidence interval; EOT = end of trial; MK-4482 = drug development code for molnupiravir; N = number of participants with Baseline and post-Baseline SARS-CoV-2 ribonucleic acid (RNA) samples at the timepoint of analysis; n = number of participants with undetectable infectious titre at each post-Baseline timepoint among negative (N.) infectivity results are imputed as undetectable if the post-Baseline sample was not sent for infectivity testing due to SARS-CoV-2 RNA titre being lower than 10^5 copies/mL.

95% CI is based on Clopper-Pearson method.

Day 3 includes post-Baseline records up to Day 4 relative to randomisation. EOT (Day 5) includes post-Baseline records from Day 5 (relative to randomisation) up to Day 7. End of treatment visits occurring earlier than Day 5 (relative to randomisation) are included in the Day 3 visit.

Table 16: Study MK-4482-001 Part 1 proportion of participants with undetectable SARS-CoV-2 infectivity titres over time nasopharyngeal sample modified intent-to-treat population

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Baseline	60/66	90.9 (81.3, 96.6)	64/67	95.5 (87.5, 99.1)	65/67	97.0 (89.6, 99.6)	66/69	95.7 (87.8, 99.1)
Day 3	60/60	100.0 (94.0, 100.0)	64/64	100.0 (94.4, 100.0)	64/64	100.0 (94.4, 100.0)	63/65	96.9 (89.3, 99.6)
EOT (Day 5)	63/63	100.0 (94.3, 100.0)	61/61	100.0 (94.1, 100.0)	64/64	100.0 (94.4, 100.0)	59/60	98.3 (91.1, 100.0)
Day 10	59/59	100.0 (93.9, 100.0)	55/55	100.0 (93.5, 100.0)	58/58	100.0 (93.8, 100.0)	62/62	100.0 (94.2, 100.0)
Day 15	59/59	100.0 (93.9, 100.0)	52/52	100.0 (93.2, 100.0)	60/60	100.0 (94.0, 100.0)	64/64	100.0 (94.4, 100.0)
Day 29	46/46	100.0 (92.3, 100.0)	44/44	100.0 (92.0, 100.0)	56/56	100.0 (93.6, 100.0)	60/60	100.0 (94.0, 100.0)

CI = confidence interval; EOT = end of trial; MK-4482 = drug development code for molnupiravir; N = number of participants with Baseline and post-Baseline SARS-CoV-2 ribonucleic acid (RNA) samples at the timepoint of analysis; n = number of participants with undetectable infectious titre at each post-Baseline timepoint among negative (N.) infectivity results are imputed as undetectable if the post-Baseline sample was not sent for infectivity testing due to SARS-CoV-2 RNA titre being lower than 10^5 copies/mL.

95% CI is based on Clopper-Pearson method.

Day 3 includes post-Baseline records up to Day 4 relative to randomisation. EOT (Day 5) includes post-Baseline records from Day 5 (relative to randomisation) up to Day 7. End of treatment visits occurring earlier than Day 5 (relative to randomisation) are included in the Day 3 visit.

Independent expert advice

The Delegate received the following independent expert advice.

1. This drug was developed in 2014, are you aware of any clinical studies or use in other viruses?

No, there are published studies in animals including non-human primates. The independent expert is not aware of any published, completed clinical studies in humans for non-SARS-CoV-2 viruses.

There are a small number of studies in other viruses, that are all in animal models, on the basis of my literature search. There may be human studies that are unpublished, but the only human studies the expert was aware of are in SARS CoV-2 infection as a Phase I

study;[40] a Phase IIa safety and tolerability study;[41] and a Phase III study sponsored by the manufacturer and reported online currently;[42] and at the American Society of Tropical Medicine and Hygiene (ASTMH) 2021 Annual Meeting held between 17 to 21 November 2021.

The parent compound (NHC) has been studied for 40 years for its mutagenic capacity.[43] As a general mutagen, including against viral RNA, the drug has been trialled either in animal models or in culture models in:

- influenza in ferrets, mice and cell culture;[44]
- Venezualan equine encephalitis virus in cell culture with Vero cells.[45] Inhibition was also seen in experiments with equine encephalitis virus and Chikungunya virus (parallel studies (Urakova 2018);[45]
- coronaviruses SARS-CoV (also known as SARS CoV-1) and MERS-CoV in human airway epithelial cells and in mice, SARS CoV-2 in cell culture with Calu-3 cells and human airway epithelial cells, and bat coronaviruses in cell culture human airway epithelial cells;[32]
- Ebola viruses in cell culture with Vero cells;[46]
- hepatitis C virus in replicon culture studies in Huh7 cells.[47]

2. Would you expect an antiviral medicine to have a greater impact on viral titres than was observed in the studies?

No, although it is important to have further data to examine this question.

The studies above, and other recent studies in animals suggest molnupiravir reduces viral load significantly. It is likely molnupiravir will have the observed effects on reducing SARS-CoV-2 viral load in humans at similar levels, and this is consistent with the Phase III clinical results. However, it is important the viral load data (most likely as Ct values on RT-PCR of nasopharyngeal swabs) are made available for review. These data are only approximations of the actual viral load - the Ct value correlates inversely with viral load, and the nasopharyngeal swabs provide only an approximately similar amount of analyte for RT-PCR. That is, the nasopharyngeal swab contains variable amounts of analyte sampled from differing parts of the upper airway, particularly when collected in different countries by different collectors. The Phase III MOVe-OUT trial included interim analysis of 775 patients from Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Israel, Italy, Japan, Mexico, Philippines, Poland, Russia, South Africa, Spain, Sweden, Taiwan, Ukraine, the United Kingdom and the United States of America. Hence it is very likely collection differed significantly between sites, and that there has been

[40] Painter, W. P. et al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2, *Antimicrob Agents Chemother*, 2021; 65 (5): e02428-20.
[41] Fischer, W. et al. Monupiravir, an Oral Antiviral Treatment for COVID-19, *MedRxiv*, 2021; 2021.06.17.21258639.
[42] https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalisation-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/.
[43] Sledziewska, E. and Janion, C. Mutagenic Specificity of N4-Hydroxycytidine, *Mutat Res*, 1980; 70 (1): 11-16.
[44] Toots, M. et al. Characterization of Orally Efficacious Influenza Drug with High Resistance Barrier in Ferrets and Human Airway Epithelia, *Sci Transl Med*, 2019; 11 (515): eaax5866.
[45] Urakova, N. et al. β-d-N4-Hydroxycytidine is a Potent Anti-alphavirus Compound That Induces a High Level of Mutations in the Viral Genome, *J Virol*, 2018; 92 (3): e01965-17.
[46] Reynard, O. et al. Identification of a New Ribonucleoside Inhibitor of Ebola Virus Replication, *Viruses*, 2015; 7 (12): 6233-6240.
[47] Stuyver, L.J. et al. Ribonucleoside Analogue that Blocks Replication of Bovine Viral Diarrhea and Hepatitis C Viruses in Culture, *Antimicrob Agents Chemother*, 2003; 47 (1): 244-254.

variation in amount of sample collected for testing and that this reduces the reproducibility of calculations of viral load.

The NHC/EIDD mechanisms of action are that molnupiravir has inhibitory effects on viral RNA dependent RNA polymerase via two major effects; firstly, as a competitive nucleoside analogue resulting in error catastrophe in a similar manner to ribavirin;[48] and favipiravir;[49] and secondly, by being incorporated into the nascent replicated RNA and then remaining as a mis-incorporated nucleoside analogue (rather than the correct cognate nucleoside).[50] These effects will be seen on *in vitro* and *in vivo* study.

3. Comment on the significance of the increased viral mutation rate detected in the clinical studies.

The independent expert's opinion is this is not significant for utility of the antiviral drug. It would be important to continue monitoring for viral mutations using whole genome sequencing of viruses in treated patients.

The increased viral mutation rate is the effect expected on administration of the antiviral molnupiravir. The results noted for Study 002 were highest rates of mutation seen at the highest dose (800 mg twice daily) on the last day of dosing (Day 5). The relevance of this should be further examine; it is likely mutation rates will be high at all doses based upon the drugs action, and that over time these will accumulate, a manifestation of Muller's ratchet resulting in loss of replication competence or 'death' of the individual virion RNA from error catastrophe.

Could these viral mutations have an impact on the epidemiology of COVID (that is to suggest, to create a more virulent strain)?

The likelihood of mutations resulting in a more virulent strain of SARS-CoV-2 from treatment with molnupiravir over the long-term has not been assessed. It is less likely, but unproven, that virus mutation induced by molnupiravir will increase virulence of SARS-CoV-2.

Virulence is the amount of damage, or severity of pathology, the SARS-CoV-2 virus causes in the human host. The effect of enhanced replication or immune escape that could theoretically result from increased SARS-CoV-2 mutation would potentially then depend upon several factors:

- the amount of increase in viral load in the respiratory tract and whether increased viral load caused more severe disease such as pneumonitis.
- whether viral mutations allowed infection of different organs (that is, increased tropism) such as enhanced neuronal tropism causing encephalitis.
- whether viral mutations, particularly in the S (Spike) protein occurred that allowed vaccine escape viruses to emerge.
- if virus emerged during treatment with molnupiravir that had enhanced stimulation of immune response (for example, a cytokine storm) that resulted in virus clearance but increased host (human lung) damage resulting in the patient's death.

Molnupiravir causes generalised mutations throughout the genome of many viruses;[45] as the major mechanism of action. The mutated viruses, in theory and practice, then become replication incompetent prior to transmission to another host. Hence all of the possible

[48] Vignuzzi, M. et al. Ribavirin and Lethal Mutagenesis of Poliovirus: Molecular Mechanisms, Resistance, and Biological Implications, *Virus Res*, 2005; 107 (2): 173-181.
[49] Hashemian, S. M. et al. A Review on Favipiravir: the Properties, Function, and Usefulness to Treat COVID-19, *Expert Rev Anti Infect Ther*, 2021; 19 (8): 1029-1037.
[50] Gordon, et al. Molnupiravir Promotes SARS-CoV-2 Mutagenesis via the RNA Template, *J Biol Chem*, 2021; 297 (1): 100770.

scenarios shown above would need to occur before virus 'death' in order for replication competent SARS-CoV-2 to be transmitted to another host. This is possible, although to date on *in vitro* and *in vivo* study in animal models, it has not been recorded.

4. Molnupiravir is not specific for COVID 19, could there be implications on other viruses?

Yes, NHC, the active component of molnupiravir has an effect against MERS, bat coronaviruses,[32] and others listed above.[51] Further, as molnupiravir is a non-specific inhibitor of molnupiravir enzymes, in theory there are many RNA viruses which use the RNA-dependent RNA polymerase replication system to grow and transmit between humans. All of these could be inhibited/affected by molnupiravir.

5. ***Other comments***

There are also issues around mammalian cell mutagenesis, as NHC acts as a mutagen in other polymerases, and has been shown *in vitro* on HPRT gene knockout assays to be mutagenic to hamster (CHO-K1) cells. This is of significant concern as firstly, the mechanism of action of molnupiravir involves insertion of the mutated base into the sequence, unlike some other antivirals with similar actions (ribavirin); secondly, such studies for mutagenesis in humans would require long-term followup for development of tumours; thirdly, animal model data are not currently available, and forthly, there are severe consequences of such mutagenesis inducing development of human tumours.

Another issue around use of a mutagen in pregnant women or those intending pregnancy has been influenced by evidence for mutagenicity in similar drugs (favipiravir).[49]

Advisory Committee considerations[52]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

The ACM advised the following in response to the Delegate's specific request for advice:

1. In the pivotal study, there was a reduction in the risk of hospitalisation in those of high risk of severe disease. However there was no significant change in COVID-19 symptoms. The primary outcome was statistically significant, but not supported by secondary outcomes. Please comment upon the mechanism behind the reduction in hospitalisation in the absence of any changes in symptom scores.

The ACM considered that the current submitted data are limited, being based on an interim analysis of Phase III data. The ACM commented that the final results of the Phase III study (MOVe-OUT [the MOVe-OUT trial]) appear to be available but have not yet been provided to the TGA for evaluation. The ACM advised that this final data should be provided to the TGA.

The ACM commented that it is plausible that based on the mechanism of action, early treatment reduces total antigen load, hence inhibiting the cytokine inflammatory response which appears to play a role in severe COVID-19.

[51] Agostini, M. L. Small-molecule Antiviral b-D-N4-hydroxycytidine Inhibits a Proofreading-intact Coronavirus with a High Genetic Barrier to Resistance, *J Virol*, 2019; 93 (24): e01348-19.
[52] The ACM provides independent medical and scientific advice to the Minister for Health and the TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre market and post-market functions for medicines. Further information can be found here: https://www.tga.gov.au/committee/advisory-committee-medicines-acm.

2. Please comment on the significance of the reduction in viral titre in the clinical studies. Is it plausible that this would cause a dramatic decrease in hospitalisations?

The ACM advised that there are currently too many unknown factors to make a clear recommendation on this question.

The ACM was of the view that viral load may not be a good surrogate for clinical outcomes, particularly as the pathogenesis for severe disease may not be related to viral damage. The ACM noted that severe disease can be caused by the body's immune response to the virus, rather than the virus itself.

The ACM discussed the limitations of correlating PCR testing and clinical outcomes within the trial and highlighted that PCR testing can detect live, defective and dead virus.

3. Should there be long-term safety studies performed to identify the impact of variants of concern? What sort of study would they be?

The ACM was of the view that additional long-term safety studies are important.

The ACM advised that animal studies on variants of concern would be beneficial.

Any available data on mutations associated with resistance, and treatment emergent mutations associated with variants of concern, for example the N501Y mutation, would also be beneficial.

The ACM noted theoretical concerns that a treatment that increases mutation rates could potentially accelerate evolutionary change in the virus. The ACM commented that Australia has good genomic surveillance through the Communicable Diseases Genomics Network, but that on- and post-treatment testing and characterisation of serial strains may also be warranted, at least for a period of time after the drug starts being administered in the community.

4. Is a negative pregnancy test be required before treatment?

The ACM was of the view that it is reasonable to have a negative pregnancy test prior to treatment with molnupiravir. However, agreed this question and the broader use in pregnancy should be further considered in the context of the final MOVe-OUT study data.

However, the ACM noted the increased risk of adverse outcomes with COVID-19 infection in pregnant women resulting in higher rates of hospitalisation and higher rates of ICU admission and need for ventilation.

The ACM highlighted potential challenges to access within a 3-day window should a negative pregnancy test be required.

5. Are the restrictions of use proposed by the Delegate reasonable, or are there public health reasons why this medicine should be more widely available. Are restrictions that should be placed on the use of this medicine?

The ACM strongly advised that given the potential carcinogenicity and reproductive toxicity concerns, molnupiravir should be restricted to a Prescription Only Medicine (Schedule 4 (S4). This would ensure that the potential risks of treatment are adequately discussed between the clinician and patient.

6. Should molnupiravir be restricted for use in just unvaccinated patients based on the lack of efficacy demonstrated in those with positive antibodies at Baseline?

The ACM noted the results of the clinical trial which show no evidence of benefit if the participant was seropositive.

The ACM commented that not all vaccinated patients will achieve a robust response to COVID-19 vaccination, including the immunocompromised.

The ACM discussed issues with easy access to antibody testing, particularly given the short window of time in which the treatment has been suggested to have efficacy.

In light of these considerations and based on the limited data, the ACM was uncertain about restricting use to just unvaccinated patients.

7. Other advice

The ACM discussed the mutagenic potential of molnupiravir. The ACM commented that long-term human follow-up for development of tumours is important.

Conclusion

The ACM was of the view that there are currently insufficient data to make a recommendation on the overall risk/benefit profile of molnupiravir for the treatment of COVID-19.

In providing this advice, the ACM acknowledged that topline efficacy data from Part 2 of the MOVe-OUT study in 1433 randomised participants has been recently reported but has not yet been evaluated by the TGA. The ACM advised that these data should be provided to the TGA.

The ACM noted the observed safety profile in the clinical trials. The ACM also considered the theoretical safety concerns in animal models related to the mechanism of action, which should be explored further. These issues are relevant to the overall risk/benefit considerations in the current Australian context.

The ACM recommended deferral of a decision by the Delegate, pending review of additional information.

Risk/benefit assessment (post-Advisory Committee Meeting)

Additional data submitted by the sponsor

Study 002

On 4 December 2021, the sponsor provided a statistical analysis of all randomised patients in Study MK-4482-002 (abbreviated as Study 002, also known as the MOVe-OUT trial).

Study 002 is a Phase II/III randomised, placebo controlled, double blind study currently being conducted to evaluate the efficacy, safety, and PK of molnupiravir in non-hospitalised adults with COVID-19. This study was comprised of 2 parts. Part 1 (Phase II, dose selection) and Part 2 (Phase III, formal evaluation of efficacy). Data from each part were analysed separately. The results from 2 interim analyses (Interim Analysis (IA)1 and 2) based on Part 1 were used in combination with results from Study 001 (Part 1) and Study 006 to select the 800 mg every 12 hours dose for further evaluation in Part 2 (Phase III) of Study 002.

Part 2 (Phase III) was designed and powered to demonstrate the efficacy of molnupiravir at the selected dose. Part 2 was initiated in May 2021, and the last participant completed their Day 29 visit in November 2021. Participants were randomised 1:1 (stratified by time from symptom onset (≤ 3 days, > 3 (4 to 5) days)) to receive either 800 mg molnupiravir or placebo orally every 12 hours for 5 days and followed for primary efficacy evaluation through Day 29.

Participants randomised in Part 2 were to have:

- Laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days prior to randomisation;
- mild or moderate COVID-19; and

- at least one characteristic (for example, age > 60 years) or underlying medical condition (for example, obesity) associated with being at increased risk for severe illness from COVID-19. All serious and nonserious AEs were to be reported through 14 days following the last dose of study intervention. All SAEs considered related (by the investigator) to study intervention during the study were to be reported.

Two interim analyses (IA3 and IA4) were planned for Part 2 (Phase III) of the study and conducted simultaneously when 50% of Phase III enrolment (775 participants of 1550 planned) were followed through the Day 29 visit. At the combined IA3/IA4 time point, the prespecified statistical criterion for success was met and the study's formal evaluation of efficacy was considered complete (the null hypothesis was rejected based on the results of the interim analysis). The sponsor has stated that the descriptive summaries of efficacy for all participants in Part 2 (Phase III) through Day 29 are considered to be supportive of the analyses reported at the IA3/IA4 timepoint. All Day 29 visits for all participants enrolled in Study 002 were completed by 4 November 2021. The clinical database was locked on 16 November 2021. This statistical report provides the top line efficacy and safety analyses for all randomised participants in Part 2 (Phase III) through the Day 29 visit in Study 002. This report contains results from descriptive efficacy and virology summaries as well as safety information for all participants randomised in Part 2 (Phase III).

The statistical analysis did not include any adjustment for multiplicity.

Results

Results for the absolute and relative risk reduction for hospitalisation or death, for both the interim and final analysis, are given in Table 18, below. Between country comparisons are given in Table 17.

Table 17: Study MK-4482-002 Absolute and relative risk reduction

	Molnupiravir	Placebo	Absolute risk reduction	Relative risk reduction
Interim analysis				
Hospitalisation or death	28/385 (7.3%)	53/377 (14.1%)	-6.8% (-11.3, -2.4)	50%
Final analysis				
Hospitalisation or death	48/709 (6.8%)	68/699 (9.7%)	-3.0 % (-5.9, -0.1)	30%

Table 18: Study MK-4482-002 Incidence of hospitalisation or death through Day 29 by country (modified intent-to-treat population);[53]

	Participants, n/m (%)		
Country	Molnupiravir N=709	Placebo N=699	Difference, % (95% CI)
Brazil	1/34 (2.9)	9/40 (22.5)	-19.6 (-35.2, -4.7)
Chile	1/20 (5.0)	2/18 (11.1)	
Colombia	10/136 (7.4)	18/139 (12.9)	-5.6 (-13.1, 1.6)
Guatemala	5/55 (9.1)	0/58 (0.0)	9.1 (2.5, 19.6)
Mexico	4/83 (4.8)	5/66 (7.6)	-2.8 (-12.4, 5.4)
Philippines	4/13 (30.8)	3/13 (23.1)	
Russian Federation	11/155 (7.1)	15/176 (8.5)	-1.4 (-7.4, 4.7)
South Africa	3/89 (3.4)	7/83 (8.4)	-5.1 (-13.5, 2.2)
Ukraine	0/59 (0.0)	2/48 (4.2)	-4.2 (-14.0, 2.1)
United States	4/41 (9.8)	5/45 (11.1)	-1.4 (-15.5, 13.2)

CI = confidence interval; m=number of participants in the modified intent-to-treat population with the corresponding group; N = population size; n=number of participants died or hospitalised through Day 29.

Primary endpoint by country (at least 20 participants enrolled) all randomised population.

Unknown survival status at Day 29 was counted as having an outcome of hospitalisation or death.

Treatment difference and 95% CI were not calculated for subgroups with small sample sizes (< 25 per treatment group) as per the protocol statistical analysis plan.

a The corresponding confidence interval is based on Miettinen and Nurminen method.

At Baseline, the severity was moderate in 44.5%. Most participants had detectable SARS-CoV-2 RNA, and 19.8% had positive SARS-CoV-2 nucleocapsid antibody results. Of those with genotypes available, the most common genotypes were delta variant 58.1%, mu variant 20.5% and gamma variant 10.7%.

There was a difference in efficacy demonstrated in different countries and with different strains. This is despite *in vitro* data suggesting it would be efficacious against all strains.

Table 19: Study MK-4482-002 Incidence of hospitalisation or death through Day 29 by clade (modified intent-to-treat population);[53]

	Participants, n/m (%)		
Clade Designation	Molnupiravir N=709	Placebo N=699	Difference, % (95% CI)
20J (Gamma)	0/37 (0.0)	9/47 (19.1)	-19.1 (-32.6, -8.9)
21H (Mu)	6/75 (8.0)	13/82 (15.9)	-7.9 (-18.5, 2.6)
21A, 21I, 21J (Delta)	18/237 (7.6)	22/221 (10.0)	-2.4 (-7.8, 2.9)
Other	5/47 (10.6)	7/38 (18.4)	-7.8 (-24.4, 7.4)
Unknown	19/313 (6.1)	17/311 (5.5)	0.6 (-3.2, 4.4)
Total	48/709 (6.8)	68/699 (9.7)	-3.0 (-5.9, -0.1)

CI = confidence interval; m=number of participants in the modified intent-to-treat population with the corresponding group; N = population size; n=number of participants died or hospitalised through Day 29.

Primary efficacy by clade all randomised population

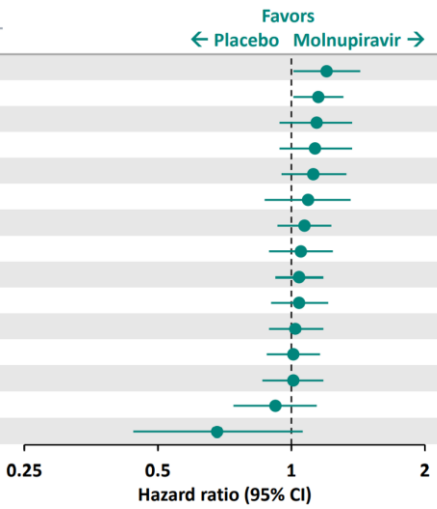
Unknown row includes participants with unavailable sequence data and participants with unknown clade designation.

[53] United States (US) Food and Drug Administration (FDA) Antimicrobial Drugs Advisory Committee (ADAC) Molnupiravir, 30 November 2021, presentation slides. Available at: https://www.fda.gov/media/154472/download.

The analysis of the secondary endpoints showed some improvement in symptom scores. However, the study was not power to detect this (see Table 20 and Table 21 below).

Table 20: Study MK-4482-002 For most signs/symptoms, sustained improvement or resolution was more likely for participants treated with molnupiravir (all randomised population);[53]

Signs/Symptoms through Day 29	Participants* Molnupiravir	Placebo	HR (95% CI)
Loss of smell	323	318	1.20 (1.01, 1.43)
Fatigue (tiredness)	528	538	1.15 (1.01, 1.31)
Shortness of breath or difficulty breathing	260	258	1.14 (0.94, 1.37)
Loss of taste	262	242	1.13 (0.94, 1.37)
Sore throat	296	318	1.12 (0.95, 1.33)
Diarrhea	166	158	1.09 (0.87, 1.36)
Nasal congestion (stuffy nose)	429	439	1.07 (0.93, 1.23)
Chills	279	308	1.05 (0.89, 1.24)
Cough	574	570	1.04 (0.92, 1.18)
Feeling hot or feverish	372	386	1.04 (0.90, 1.21)
Headache	429	472	1.02 (0.89, 1.18)
Muscle or body aches	454	460	1.01 (0.88, 1.16)
Rhinorrhea (runny nose)	347	348	1.01 (0.86, 1.18)
Nausea	171	176	0.92 (0.74, 1.14)
Vomiting	38	49	0.68 (0.44, 1.06)

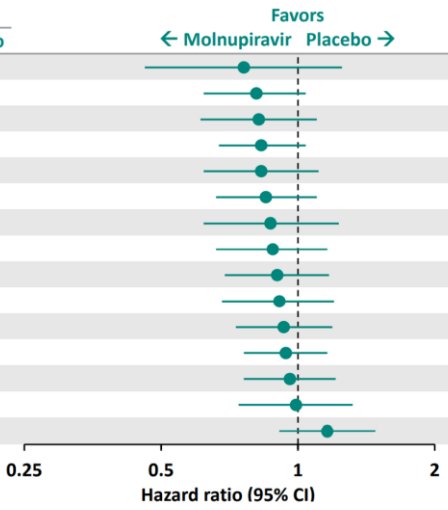


CI = confidence interval.

* Number of participants who had the corresponding sign/symptom at Baseline.

Table 21: Study MK-4482-002 For most signs/symptoms, progression was less likely for participants treated with molnupiravir (all randomised population);[53]

Signs/Symptoms through Day 29	Participants* Molnupiravir	Placebo	HR (95% CI)
Vomiting	702	692	0.76 (0.46, 1.25)
Loss of smell	385	372	0.81 (0.62, 1.04)
Diarrhea	695	691	0.82 (0.61, 1.10)
Cough	688	672	0.83 (0.67, 1.04)
Feeling hot or feverish	676	673	0.83 (0.62, 1.11)
Nasal congestion (stuffy nose)	682	664	0.85 (0.66, 1.10)
Chills	679	676	0.87 (0.62, 1.23)
Sore throat	695	681	0.88 (0.66, 1.16)
Rhinorrhea (runny nose)	694	690	0.90 (0.69, 1.17)
Loss of taste	461	433	0.91 (0.68, 1.20)
Headache	640	640	0.93 (0.73, 1.19)
Shortness of breath or difficulty breathing	701	681	0.94 (0.76, 1.16)
Fatigue (tiredness)	659	637	0.96 (0.76, 1.21)
Nausea	688	686	0.99 (0.74, 1.32)
Muscle or body aches	655	640	1.16 (0.91, 1.48)

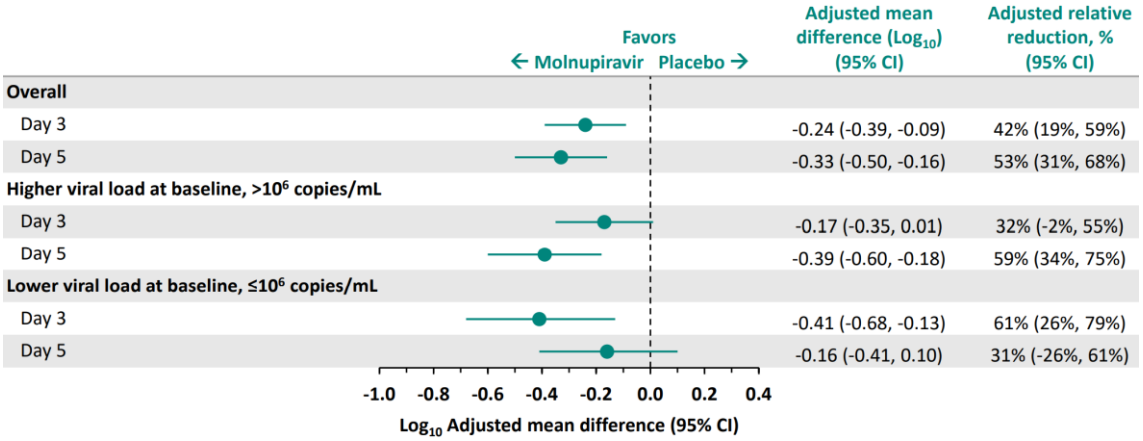


CI = confidence interval.

* Number of participants who had absent or non-severe sign/symptom at Baseline.

There was a reduction of viral loads on Days 3 and 5. The significance of a -0.24 log reduction in viral load is unknown. In the sponsor's statistical analysis plan, it states that a one log reduction in viral load is considered to be clinically significant.

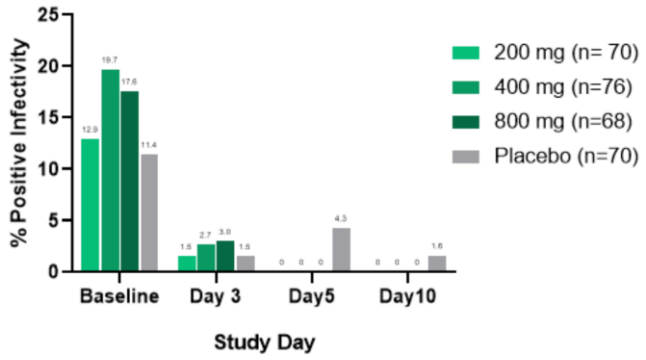
Table 22: Study MK-4482-002 Treatment with molnupiravir was associated with a greater decrease in mean SARS-CoV-2 ribonucleic acid from Baseline to Days 3 and 5 (all randomised population);[53]



CI = confidence interval; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

There was no virus detected beyond Day 5 in the molnupiravir group, however low number of virus were also detected in the placebo group.

Figure 8: Study MK-4482-002 Recovery of infectious virus over time;[53]



n = sample size.

No infectious virus was recovered from any molnupiravir treated participant by Study Day 5 and Day 10.

In the sponsor's clinical study plan for provisional registration, it states that the full study report for the 29-day data for the full study population will be available in the first quarter of 2022, and the 7 month data in the third quarter of 2022.[35] It is not clear which data set the sponsor will apply for full registration.

Delegate's further consideration of the issues discussed at the Advisory Committee Meeting

Mutagenicity

- There is a concern that the mechanism of action of molnupiravir is such that there is the possibility of it inducing error in mammalian mRNA.
- *In vitro* genotoxicity assessment in bacteria (Ames) was positive.
- an *in vitro* study in human lymphoblastoid TK6 cells was negative.

- A (non-Good Laboratory Practice (GLP);[54] compliant) *in vitro* study in Chinese hamster cells was positive.
- An *in vivo* rat micronucleus study showed no evidence of chromosomal damage.
- An *in vivo* 28-day rat pig-a mutation assay was equivocal.
- The 28-day big blue transgenic rodent mutation assay showed no increase in mutation frequency in the liver or bone marrow. This is considered to be the gold standard assay for *in vivo* mutagenesis.
- A short duration of use is considered to make this medication low risk in terms of mutagenicity.

Outstanding questions

- How good do animal models of mutagenicity correlate with the risk to humans?
- Can it be for certain that a short duration of use has a low risk long term cancer?

Use in pregnancy, need for pregnancy test and contraception

Molnupiravir is a teratogen. It should not be used in pregnancy. Women of childbearing age are generally at low risk of severe COVID-19, unless they have other risk factors such as obesity, poorly controlled diabetes or asthma or respiratory disease. There was considerable discussion and concern about potential teratogenicity at the ACM.

The Delegate agrees with the RMP evaluator that a pregnancy test should be recommended in women of childbearing age who are sexually active and are not using a reliable form of contraception.

The Delegate would also advocate for a black box warning in the PI and Consumer Medicine Information (CMI) to highlight this important issue.

Further questions for the sponsor

1. What additional data do you plan to submit prior to provisional approval? When will the final study report including protocol, methods, subgroup analysis, be available?

Except for data from the full population of participants randomised in Study P002 Part 2 and followed through Day 29, which was submitted to the TGA via the Study P002 Part 2 statistical report,[55] no additional clinical data are planned for the submission supporting consideration of provisional registration. The final study report for Study P002 Part 2 through Day 29, which will include the protocol, methods and subgroup analyses, is in progress and is expected to be finalised and available for submission in the first quarter of 2022.

At the time of the initial submission to TGA and to the Food and Drug Administration (FDA), data from the full population of participants randomised in Study P002 Part 2 were not available. These data became available to the sponsor and were subsequently shared with TGA via submission of the Study P002 Part 2 statistical report on 6 December 2021 as well as submission of the addendum to the FDA Advisory Committee Meeting Briefing Book on 26 November 2021. New analyses of clinical trial data presented in the FDA slides at the Advisory Committee Meeting that were not included in the initial submission to TGA (nor the initial submission to the FDA) were from the full population for Study P002 Part 2. With the exception of the display of the primary endpoint for the post-interim analysis

[54] **Good Laboratory Practice** is a code of standards following the International Council on Harmonisation (ICH) relevant to testing of medicines in laboratories during drug development.
[55] Inclusion of this information is beyond the scope of the AusPAR.

population only in the FDA's slide,[56] all clinical study analyses presented by the FDA are included in the Statistical Report. The sponsor has verified the accuracy of the data presented in FDA's slide.[56]

It should be noted that there were no prespecified plans to perform separate analyses of only data from the post-interim analysis population. The post-interim analysis data reflect a subset of data from a discrete period of time during a highly dynamic global pandemic and therefore likely reflect the evolving nature of the pandemic.

2. What additional data do you plan to submit prior to full approval?

The clinical study report for all Part 2 participants followed through Day 29 in the MOVe-OUT trial (Study P002) will be submitted to TGA in approximately in the first quarter of 2022 prior to full approval. Additional virology data will be summarised in a separate virology report which will be available in approximately March 2022. No other additional clinical data is planned for submission to support full approval.

A final clinical study report will also be authored following completion of the 7-month follow-up visit which will include a summary of any hospitalisations or deaths in Part 1 or Part 2 participants occurring after the Day 29 visit through 7 months from the last dose of study intervention. There are no formal analyses planned for the 7-month timepoint and is therefore not considered supportive of full approval. This clinical study report will be available in approximately in the fourth quarter of 2022.

3. In the statistical analysis plan, it is stated that a one log difference in viral load is clinically significant. Please justify the clinical significance of a 0.2 to 0.3 reduction in viral load that is detected only for a few days. Is there any data about the correlation between viral load by day and clinical outcomes?

The one log-unit difference in RNA change from Baseline in SARS-CoV-2 RNA titres was a statistical assumption to be employed in Part 1 of the study while assessing the dose-response relationship of molnupiravir. The clinical relevance of this threshold was postulated early in the pandemic when the scientific community was still learning about SARS-CoV-2 viral RNA dynamics and kinetics, and this one log-unit difference reduction target was only an estimate based on what has previously been observed to demonstrate efficacy with other antivirals (for example, for treatment of HIV).

In both Study P002 Part 1 and Part 2, a modest but greater reduction in the mean SARS-CoV-2 RNA was observed in the molnupiravir 800 mg group compared with placebo in participants who initiated treatment within 5 days of symptom onset. In addition, the antiviral effect of molnupiravir was further supported by an observed increase in the SARS-CoV-2 RNA error rate as predicted by molnupiravir's mechanism of action. However, the complex relationship between SARS-CoV-2 viral replication, the host immune response, and viral RNA clearance is still being explored in the scientific community. SARS-CoV-2 RNA measurements from nasopharyngeal swabs can be variable and titres do not always correlate with disease severity at Baseline or the risk of progression to severe disease, and may not correlate with the SARS-CoV-2 viral load at other anatomical sites of infection (that is, bronchoalveolar lavage or oropharyngeal specimens.[60] Of note, qualitative and quantitative SARS-CoV-2 virology testing is still in progress for Study P002 participants, and the full set of virology data is expected to be available by March 2022 and will be summarised in a separate virology report.

[56] United states Food and Drug Administration (FDA), FDA Introductory Remarks, Antimicrobial Drugs Advisory Committee Meeting November 30, 2021, Slide 20 - P002 Efficacy Analysis. Available at: https://www.fda.gov/media/154473/download.

4. ***It is noted that there was a range in the change in symptom scores, and that the severity scores and duration scores for the same symptoms did not correlate. The study was not powered to analyse this. In addition, there was no adjustment for multiplicity. How sure can it be considered sure that it did not occur by chance?***

Self-reported sign/symptoms were assessed aligned with the FDA Guidance for Industry.[57]

The success of this study is based on a single primary endpoint (a composite of hospitalisation or death) and a single treatment comparison (molnupiravir 800 mg versus placebo). There were no adjustments for multiplicity planned for secondary endpoints. The analyses of self-reported sign/symptom data were used as supportive evidence for the primary endpoint. The study was not designed to draw any statistical inference from these secondary endpoints.

The secondary endpoints were 'time to sustained resolution or improvement' and 'time to progression' for each of the 15 targeted self-reported sign/symptom, separately. To ensure a robust assessment of these two endpoints for each targeted self-reported sign/symptom, both the severity-based assessment (improvement/resolution or progression) and the duration (time to event) of each symptom were defined with the following considerations:

To ensure the observed improvement was not due to the potential day-to-day fluctuation of the symptom severity, for each targeted self-reported sign/symptom present (that is, not rated 'none' or 'no') at Baseline/randomisation, the time to sustained resolution or improvement was defined as the first of 3 consecutive days when resolution or improvement (that is, symptom severity was rated lower compared to Baseline) was demonstrated. The duration of 3 consecutive days was chosen as it was considered by sponsor to be a clinically relevant timeframe to define sustained improvement. This definition was agreed upon by the US FDA. Many patients who remain in the outpatient setting are anticipated to recover from COVID-19 without intervention; therefore, measurement of improvement based on 3 days of sustained improvement is expected to provide a relevant differentiation of response that is attributable to use of a short course of antiviral treatment. To be counted as sustained improvement or resolution, the symptom must not relapse by Day 29 (that is, with 2 or more consecutive days of symptom severity returning to the baseline rating or worse).

Since evaluation of COVID-19 signs/symptoms via a 'time to sustained resolution or improvement' analysis would not account for symptoms that may have developed during progression of the disease, a 'time to progression' analysis was included to provide a full evaluation of all signs/symptoms reported by participants. For each of the targeted self-reported signs/symptoms not rated as 'severe' or 'yes' at Baseline/randomisation, time to progression was defined as the number of days from randomisation to the first of 2 consecutive days when the sign/symptom worsened (that is, symptom severity was rated higher compared to Baseline).

5. ***In relation to mutagenicity, can it be certain that 5-day use will not associated with cancer? How good are animal models?***

The sponsor considers that molnupiravir has minimal risk for carcinogenicity under the proposed conditions of clinical use, given that molnupiravir was shown to be non-genotoxic and non-mutagenic *in vivo* in mammalian systems.

The mutagenic and genotoxic potential of molnupiravir was comprehensively assessed in standard and follow-up *in vitro* and *in vivo* assays conducted in accordance with

[57] U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment, Guidance for Industry, September 2020.

international regulatory guidelines. The genotoxicity assessment covered all endpoints (chromosome damage, chromosome loss, mutagenicity) as recommended per international guidelines.

While molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation, the lack of mutagenicity in *in vivo* mutagenicity assays provide strong evidence that the *in vitro* mutagenicity is not relevant to *in vivo* mammalian systems.

The sponsor utilised *in vivo* mutagenicity assays specifically designed to understand mutagenicity *in vivo* (Pig-a mutagenicity assay in rats and Big Blue (cII Locus) transgenic rat assay). These assays followed strict methodology established through multi-agency alignment in OECD and international expert bodies and provide weight of evidence according to principles such as those outlined in ICH S2R1 and WHO guidance/expert opinion documents. It is important to note that the rats were administered molnupiravir at doses up to the maximum tolerated dose, 500 mg/kg/day, and for longer durations (28 days) than the proposed short-term 5-day clinical administration of molnupiravir in humans. Based on an analysis by Zeller et al;[58] (transgenic rodent mutation assays have demonstrated approximately 90% sensitivity in detecting human carcinogens: 28/31, and slightly higher sensitivity (93%) when combined with the negative micronucleus test results as in the case of molnupiravir (see below). Similar results were described in a detailed review paper;[59] submitted to OECD to support OECD Test Guideline No. 488 showing 92% positive predictive value of the transgenic rodent assay for 154 rodent carcinogens.

In addition, molnupiravir did not induce chromosome damage or chromosome loss in an *in vitro* micronucleus assay in the human TK6 cell line using short incubation (4-hour; with and without an exogenous metabolic activation system) and long incubations (27-hour; without an exogenous metabolic activation system) tested up to 1 mM, or in an *in vivo* micronucleus assay in rats administered molnupiravir up to the limit dose of 2000 mg/kg/day for 2 days.

In conclusion, the comprehensive genotoxicity assessment in robust and well-characterised standard regulatory assays indicates molnupiravir has low risk for genotoxicity and carcinogenicity.

Delegate's further considerations before a final regulatory discussion is made

- It is not entirely clear what additional data will be available before the sponsor requests full approval. Long term clinical studies to assess the potential for mutagenicity may not be available.
- The results of the animal studies do not entirely match the results of clinical studies in terms of viral load reduction and efficacy. The *in vitro* studies suggested efficacy against a range of variants but in the clinical studies there was variable efficacy against different variants.
- In general, for medication to be approved based on a single clinical study the study needs to be robust and the results unequivocal. There has been some relaxation of the requirements for registration based on unmet need in the context of the current pandemic. However, with the number of active cases in Australia being well controlled with the available vaccines, and a number of other medications available for early

[58] Zeller, A. et al. A Critical Appraisal of The Sensitivity of *in vivo* Genotoxicity Assays in Detecting Human Carcinogens, *Mutagenesis*, 2018; 33 (2): 179–193,
[59] Lambert I. B. et al. Detailed Review of Transgenic Rodent Mutation Assays, *Mutat Res*, 2005; 590 (1-3): 1-280.

disease. The Delegate is unsure if the relaxation of the TGA's usual standards is warranted.

- Consultation with a virologist/infectious disease consultant regarding the results for viral load reduction and efficacy against variant.
- Consultation with an oncologist or toxicologist regarding the relevance of the animal studies and need for further studies to investigate the mutagenicity.
- Consideration of the need for a black box warning.

Delegate final decision regarding provision registration

Discussion of outstanding issues post-Advisory Committee Meeting

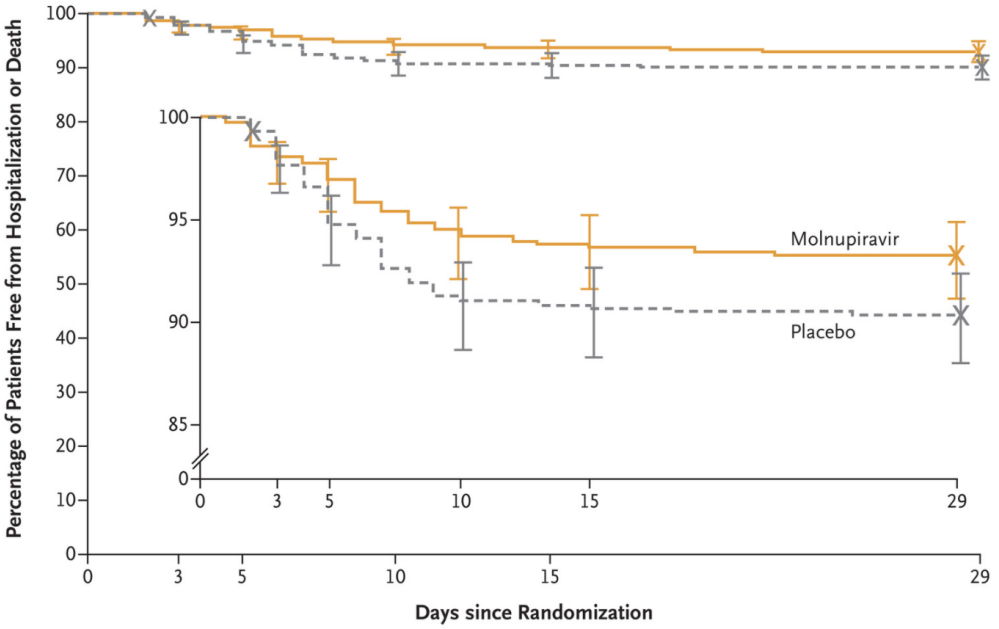
The differences in results from the interim to the final analysis

Between the interim and final analysis, there was less difference in hospitalisations and deaths between the molnupiravir group and the placebo group. This was largely driven by a lower rate of events in the placebo group, suggesting the patient population in the second part of the study did not become as unwell.

The sponsor's response from the 7 January 2022 provided some additional information about possible reasons for the difference in efficacy seen. These include:

- Lower event rate in the placebo group at final analysis
  - there were more female participants in the final analysis than the interim analysis, females participants are less likely to get severe disease;
  - less participants with high viral load at final analysis. Higher viral load is more likely to cause severe disease; and
  - less Hispanic, more Europeans participants. The Hispanic population have higher risk of severe disease.
- Differences between placebo and active group:
  - Less Hispanics participants in placebo group (25% compared with 33%)
  - More patients with positive SARS-CoV-2 antibodies in the placebo group (27% compared with 19%)
  - Low number of patients with high viral load (31% compared with 37%)

Figure 9: Time-to-event analysis of hospitalisation or death through Day 29 (modified intention-to-treat population);[60]



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

No. = number.

Shown are Kaplan-Meier curves with 95% confidence intervals (I bars). X indicates censored values. Data for the single participant with unknown survival status and no hospitalisation reported were censored on the day when the participant was last known to be alive. The inset shows the same data on an expanded y axis.

The overall analysis demonstrated a statistically significant difference in hospitalisation and death between the molnupiravir and placebo groups. The differences were first noted about 3 days after starting treatment and continued for 30 days.

It is also important to note that the patient population was very select for COVID-19 positive within 5 days of symptoms, unvaccinated patients, with risk factors for severe disease but unlikely to be hospitalised within 2 days.

At this time there remains some missing information in relation to baseline antibody tires, viral loads, clade designation. The Delegate notes the FDA decision letter included a requirements of the sponsor to conduct a thorough investigation into the efficacy observed in the first and second half of Part 2 of Study 002. The preliminary report is due no later than 31 March 2022, the final report incorporating serology is to be submitted no later than 30 September 2022.

This table;[61] shows a large difference in hospitalisation between countries. There were more hospitalisations in countries of lower socioeconomic status, thus it is more likely to find a benefit in these patient populations. It is also possible that the variants that circulated at the time had an impact on results.

[60] Bernal, A. J. et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients, *N Engl J Med*, 2021; NEJMoa2116044.
[61] The table has been redacted due to ongoing nature of the study, and small size of treatment groups in some countries with those countries having only patients randomised to either molnupiravir; or placebo.

On 7 January 2022, the sponsor provided some further post-hoc analysis from the final data. This showed less oxygen use, a faster improvement in C-reactive protein, and earlier improvement of oxygenation.

Table 23: Study MK-4482-002 Part 2 Mean change (standard deviation) in C-reactive protein from Baseline over time (all participants as treated population)

			Baseline		Value		Mean Change	
Visit	Treatment	N	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]	Mean (SD)	[Min, Max]
C Reactive Protein (mg/L)								
Day 3	MK-4482 800 mg	625	20.18 (50.77)	[0.19, 927.00]	18.75 (40.35)	[0.10, 501.30]	-1.44 (31.28)	[-425.70, 171.30]
	Placebo	622	17.36 (32.13)	[0.19, 264.90]	19.28 (38.74)	[0.19, 289.80]	1.92 (27.12)	[-184.90, 169.00]
EOT (Day 5)	MK-4482 800 mg	623	19.30 (49.93)	[0.19, 927.00]	15.34 (31.95)	[0.10, 300.10]	-3.96 (43.59)	[-774.60, 125.60]
	Placebo	614	16.96 (31.36)	[0.19, 264.90]	19.22 (38.37)	[0.19, 403.60]	2.26 (40.14)	[-249.30, 310.60]
Day 10	MK-4482 800 mg	591	19.46 (49.97)	[0.19, 927.00]	9.85 (22.83)	[0.03, 220.20]	-9.61 (52.66)	[-920.80, 214.70]
	Placebo	589	16.40 (31.07)	[0.19, 264.90]	13.09 (29.03)	[0.19, 279.80]	-3.31 (39.25)	[-227.40, 272.30]
Day 15	MK-4482 800 mg	600	20.19 (51.38)	[0.19, 927.00]	7.47 (22.94)	[0.10, 300.10]	-12.72 (53.22)	[-918.20, 272.00]
	Placebo	593	16.82 (32.12)	[0.19, 264.90]	7.52 (20.87)	[0.00, 233.60]	-9.30 (35.22)	[-232.70, 226.10]
Day 29	MK-4482 800 mg	585	20.45 (51.13)	[0.19, 927.00]	5.76 (12.80)	[0.08, 150.70]	-14.69 (51.53)	[-921.42, 133.30]
	Placebo	585	17.16 (32.30)	[0.19, 264.90]	4.85 (10.56)	[0.10, 125.60]	-12.32 (32.87)	[-264.00, 105.30]

EOT = end of trial; Max=maximum; Min=minimum; MK-4482 = drug development code for molnupiravir; SD=Standard deviation.

Baseline is defined as last value obtained prior to the first dose of study treatment during treatment phase. A Baseline and treatment value are required for a participant to be counted at a time point.

Table 24: Study MK-4482-002 Part 2 Summary of oxygen therapy through Day 29 (modified intent-to-treat population)

	MK-4482 800 mg n (%)	Placebo n (%)
Participants in population	709	699
No oxygen therapy	667 (94.1)	636 (91.0)
Any oxygen therapy	42 (5.9)	63 (9.0)
Conventional oxygen therapy	36 (5.1)	52 (7.4)
Oxygen therapy, high flow heated and humidified device	10 (1.4)	11 (1.6)
Non-invasive mechanical ventilation	2 (0.3)	7 (1.0)
Invasive mechanical ventilation	4 (0.6)	11 (1.6)

MK-4482 = drug development code for molnupiravir; n = sample size.

Participant can be counted in more than one category.

Delegate comment

The results of the final analysis showed a lower relative efficacy than the interim analysis. The effect size if moderate, however the results remain statistically significant. Post-hoc analysis showed additional benefits in a reduction in the need for oxygen therapy and a more reduction in C-reactive protein. The lower efficacy in the second part of the study seems to be due to a study population that was less likely to develop severe disease.

The final results of the MOVe-OUT trial will help define which patients are more likely to benefit from molnupiravir. The sponsor has an ongoing commitment to the FDA in relation to ongoing studies to determine the efficacy against circulating variants.

Reduction in viral load

The sponsor was asked to respond to the discrepancy between what was said to be a clinically significant viral load reduction in the SAP (one log unit) and what was found in the clinical studies (0.2 to 0.3 reduction).

The sponsor explained that the one log reduction was chosen early in the pandemic when little was known about SARS-CoV-2 dynamics and kinetics.

The sponsor acknowledged that there is a complex relationship between SARS-CoV-2 viral replication, the host immune response and viral clearance, and that this is not yet well understood.

There is known to be high variability and error in the measurements of SARS-CoV-2 RNA measurements from swabs, due in part to the way in which they are collected. There is also a lack of correlation between viral load and disease severity, or viral load at other anatomical sites.

Delegate comments

The Delegate notes the inherent inaccuracies of swabs to determine viral loads, and in the uncertainty about the relevance of viral load to the outcome of patients with COVID-19. The available data suggests some reduction in viral load Days 3 to 5. It is plausible, but uncertain, that the efficacy of molnupiravir is due to this.

Potential for carcinogenicity

The sponsor has completed the required studies to assess the risk of mutagenicity. Overall, the TGA's nonclinical evaluator made the following comments in relation to carcinogenicity:

'Molnupiravir and NHC were mutagenic in the bacterial assay (with and without metabolic activation). Molnupiravir and NHC were not genotoxic in in vitro and in vivo micronuclei tests, and in vivo mutation assay at the cII locus (in Big Blue Transgenic F344 Rats). Equivocal results were obtained in an in vivo Pig-a mutagenicity assay. Molnupiravir and NHC is considered to have a low risk of genotoxicity from the proposed short-term clinical use.

Carcinogenicity studies are not generally required for drugs for short term clinical use. However, the sponsor has initiated a short-term carcinogenicity in transgenic mice.'

However, clinicians on the ACM and other invited expert clinicians remain concerned about the potential use of mutagenesis based on the mechanism of action of the drug.

Delegate comments

Molnupiravir will be prescribed for 5 days only. It is most likely to be used in older adults with other risk factor for severe disease.

There is no data about use in children. Based on the mechanism of action, and the theoretical concerns about mutagenicity and the risk of cancer, the Delegate recommends against the use of molnupiravir in children.

Issues in relation to pregnancy and reproduction

The Delegate notes the variable agency response for use in pregnancy.

The MHRA Product Information states that women of childbearing potential must use an effective form or contraception during and for 4 days after treatment. They have not made a recommendation in relation to the need for a pregnancy test before treatment.

The FDA have recommended clinical judgement be made regarding the need for a pregnancy test. They have recommended females that are sexually active and of child bearing potential use contraception during treatment and for 4 days afterwards.

The FDA have also recommended that heterosexual males that are sexually active use contraception during treatment and for 3 months after. This is based upon the unknown risks the germ cells in the testis.

The nonclinical evaluator made the following comments about the risks of embryofetal development:

'Based on the submitted data, there is a risk of adverse effects on embryofetal development (e.g. [for example] *post-implantation loss, fetal malformations). Pregnancy Category D is considered appropriate. It is recommended that molnupiravir should not be taken by pregnant women. No treatment-related effects were observed in a pre-/postnatal study in*

rats. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir and therefore, breastfeeding is not recommended during treatment and for 4 days after the last dose of Lagevrio.'

The Delegate notes the FDA post-market requirement to detect PK study in rats to establish if NHC or NHC-5'-triphosphate is detected in the testes, and if it is detected in the testes, to conduct a study of germ cell mutations.

The FDA have also requested that the sponsor to maintain a pregnancy surveillance program to collect information through telephone and online reporting of pregnancies and collect outcomes for individuals who are exposed to molnupiravir during pregnancy.

Delegate comments

The sponsor has not agreed to include a black box warning. They have agreed to include a statement in relation to the need to consider a pregnancy test in women of childbearing potential who are sexually active.

The Delegate has discussed the issue of the need for contraception in males with an expert of drugs in pregnancy. In view of the uncertainty about the risk to the germ cells of the testes, the sponsor is requested to align the advice in the Australian PI to that of the FDA PI in this regard. The need for this advice will be revised when the results of the above studies in rats are available.

It will be important that health care professionals are advised of these potential concerns so that they can make a risk based assessment of the benefits and risks of molnupiravir for individual patients they are treating.

Variants of concern

The Delegate notes the FDA have included the following conditions in their letter for Emergency Use Authorization:

- that the sponsor submits the complete viral shedding results and full genome SARS-CoV-2 nucleotide sequencing results from the full randomised population in Study 002 Part 2. These included post treatment samples with viral RNA levels over 100,000 copies/mL. cell culture infectivity assessments should be conducted for any clinical specimens in which amino acid changes were detected in the SARS-CoV-2 spike protein;
- that the sponsor establishes a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2;
- that the sponsor complies with a request from the FDA to assess molnupiravir against a variant of concern;
- and that the sponsor provides sample of molnupiravir to the US Department of Health and Human Services to for evaluation of activity against emerging viral variants.

The TGA would be also interested in the results of these studies.

Delegate response to the third round of risk management plan evaluation

At the end of the RMP evaluation, the following summary of safety concerns were identified:

- Important identified risks: none
- Important potential risks: none
- Missing Information: safety in pregnancy and lactation.

The Delegate has considered the recommendations of the RMP evaluator and have made the following conclusions.

The important potential risk of embryofoetal toxicity and teratogenicity.

The sponsor has disputed the claim that molnupiravir is a teratogen based upon the pre-clinical studies that only showed fetal malformations in one rat study where there was a high exposure to molnupiravir, the other animal studies did not show any malformations. The sponsor has agreed to a pregnancy register and ongoing nonclinical studies.

The Delegate therefore accepts safety in pregnancy and lactation missing information. However, the Delegate requests that the sponsor include all of the ongoing studies examining this as part of the RMP so that is clear how this information is being gathered.

Bone marrow toxicity

The Delegate noted the toxicity demonstrated in animal models. There was no toxicity demonstrated in the clinical studies, however subjects with low platelet count and white cell count were excluded. The Delegate noted MHRA requested that bone marrow toxicity be included as an important potential risk and a post-authorisation safety studies (PASS) was recommended. However, in the sponsor's response to an overseas regulator's questions in December 2021, it states that MHRA recommendation for PASS to assess bone marrow toxicity was recommended prior to the final results of Study 002, and that such a study may no longer be recommended.

The sponsor is committed to report any bone marrow toxicity in the PSUR.

The Delegate accepts not including this as a potential risk.

Use in paediatrics

The sponsor has not applied to use molnupiravir in children.

The sponsor has stated that it is planning a juvenile animal toxicology study prior to an application for use in children.

There were findings in a nonclinical study of molnupiravir in rapidly growing rats after 3 months of use at 5.4 times the clinical exposure. These studies are not considered relevant to humans as rapidly growing rats are not a good model for bones, and the duration of exposure was far greater than is proposed in adults. There was no bone or cartilage toxicity observed in a study in rats for one months or studies in other animals.

Comments about conversion to full registration

This decision in relation the provisional registration of molnupiravir was based upon the analysis of data available at this time, in the context of the current COVID-19 pandemic. The risk benefit assessment was considered positive at this time.

However, a Delegate making a decision in relation to the full registration of this product is likely to require a greater degree of certainty about the efficacy and safety of this product. The Delegate notes the current study plan for full registration includes only the final results of the MOVe-OUT trial. The Delegate suggests the sponsor consider expanding the data submitted prior to full registration to include:

- final analysis of the MOVe-OUT trial;

- Any ongoing studies regarding potential teratogenicity in pre-clinical and clinical studies;
- ongoing studies regarding efficacy against different variants;
- ongoing studies regarding the impact on variants of concern;
- efficacy in a real world setting.

Requirements of sponsor prior to provisional registration is approved

Prior to approval of provisional registration, it is required for the sponsor to:

- respond to Delegate's recommendations in relation to the PI;
- respond to the Delegate's recommendations in relation to the CMI;
- update the RMP to include to include the post market studies that have been recommended by the European Medicines Agency (EMA) and FDA in relationship to these potential concerns.
  - Updated ASA was agreed with TGA to be submitted within 3 months following approval, not before provisional registration approval.
- provide the TGA with a Dear Health Care Provider letter explaining:
  - the differences in labelling;
  - that molnupiravir has provisional registration, and that further information about this use will be available over the next few years;
  - the need for clinicians to consider the potential benefits and risks of molnupiravir in patients with COVID-19 and risk factors for severe disease (such as obesity, diabetes, chronic lung disease, cardiac failure);
  - the need to consider a pregnancy test in women of childbearing potential;
  - the need for contraception in women of childbearing potential for the duration and treatment and 4 days after the last dose due to concerns about the risks to the developing fetus seen in animal studies, and the lack of available data in humans;
  - the need for contraception in men of childbearing potential for the duration of treatment and 3 months after due to the unknown impact of molnupiravir on the germ cells in the testes;
  - the need to provide patients with a CMI at the time of prescribing.

Proposed conditions of registration

Periodic safety update report requirement

> *Reports are to be provided in line with the UK reference dates and frequency of submissions, until the published list of EU reference dates and frequency of submission of PSURs become available. After that reports should be provided in line with the published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer.*
>
> *The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.*

In additional to the submission of PSURs, expedited Lagevrio monthly summary safety reports (including safety data for patients in Australia and reporting of Australia specific safety concerns) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

These PSURs should contain relevant information from the pregnancy surveillance program.

Black triangle

Molnupiravir (Lagevrio) is to be included in the Black Triangle Scheme. The PI and CMI for Lagevrio must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Full registration

Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided for full registration

Specifically, the sponsor must conduct studies as described in the clinical study plan submitted on 25 November 2021. The following study report(s) should be submitted to TGA:

- *MOVe-OUT (P002), to be submitted first quarter 2022 for safety and efficacy, and 7-month follow up to be submitted third quarter 2022,*[35]
- *Further guidance for sponsors is available on the TGA website.*

The sponsor is required to provide the TGA with the following information as it arises:

- data in relation to the activity of molnupiravir against global SARS-CoV-2 variants of concern including the omicron variant;
- the preliminary report for Study 002 Part 2 is due no later than 31 March 2022, the final report incorporating serology is to be submitted no later than 30 September 2022;
- results of the PK study in wild type Fisher 344 rats to determine if NHC or NHC-5'-triphosphate is detected in the testes. If this study shows that NHC is detected in the testes, the sponsor should also submit the results of the Big Blue rat study;
- results of the 6 month Tg RasH2 mouse carcinogenicity study (initiated in August 2021);
- results of the i*n vitro* resistance selection study.

The sponsor must ensure that the CMI and PI is available in electronic format for health practitioners and patients to download.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Lagevrio (molnupiravir) 200 mg, capsule, bottle, indicated for:

Lagevrio (molnupiravir) has provisional approval for the treatment of adults with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk for hospitalisation or death (see Section 5.1 Pharmacodynamic properties - Clinical trials).

The decision to approve this indication has been made on the basis of the analysis of efficacy and safety data from a Phase 3 trial. Continued approval of this indication depends on additional data.

Specific conditions of registration applying to these goods

- Risk management plan

  Molnupiravir (Lagevrio) is to be included in the Black Triangle Scheme. The PI and CMI for Lagevrio must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

  Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

  The Lagevrio EU-risk management plan (RMP) (version 0.1, dated 14 October 2021, data lock point 18 September 2021), with Australian specific annex (ASA) (version 0.2, dated 14 December 2021), included with Submission PM-2021-03679-1-2, to be revised to the satisfaction of the TGA, will be implemented in Australia.

  The sponsor should provide updates to the RMP and ASA to include ongoing post market safety studies and pharmacovigilance activities within 3 months of approval.

  [Periodic safety update reports] are to be provided in line with the UK reference dates and frequency of submissions, until the published list of EU reference dates and frequency of submission of PSURs become available. After that reports should be provided in line with the published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter, or the entire period of provisional registration, whichever is longer.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

  In addition to the submission of PSURs, expedited Lagevrio monthly summary safety reports (including safety data for patients in Australia and reporting of Australia specific safety concerns) are to be provided for the first 6 months post registration, and thereafter at intervals specified by the TGA.

- The sponsor is required to provide the TGA with the following information as it arises:
  - Data in relation to the activity of molnupiravir against global SARS-CoV-2 variants of concern including the omicron variant
  - Any additional information from further analysis of the data obtained from Study MK-4482-002 Part 2 [by the second quarter of 2022]
  - Results of the PK study in wild type Fisher 344 rats to determine if NHC or NHC-5'-triphosphate is detected in the testes. If this study shows that NHC is detected in the testes, the sponsor should also submit the results of the Big Blue rat study.
  - Results of the 6-month Tg RasH2 mouse carcinogenicity study (initiated [in the third quarter of 2021)

  - Results of the *in vitro* resistance selection study
- The sponsor must ensure that the CMI and PI is available in electronic format for health practitioners and patients to download.
- Confirmatory trial data (as identified in the sponsor's plan to submit comprehensive clinical data on the safety and efficacy of the medicine before the end of the 6 years that would start on the day that registration would commence) must be provided for full registration.

  Specifically, the sponsor must conduct studies as described in the clinical study plan submitted on 25 November 2021. The following study report(s) should be submitted to TGA:

  - MOVe-OUT ([Study] P002), to be submitted [by the first quarter of 2022] for safety and efficacy, and 7-month follow up to be submitted [by the third quarter of 2022].[35]

  Further guidance for sponsors is available on the TGA website.

Attachment 1. Product Information

The PI for Lagevrio approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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