Emergency Use Authorization (EUA) for Molnupiravir 200 mg Capsules

Center for Drug Evaluation and Research Review Memorandum

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	000108
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Merck Sharp & Dohme., a subsidiary of Merck & Co., Inc. 1 Merck Drive PO Box 100 Whitehouse Station, NJ 08889-0100 908-423-1000 POC: Sushma Kumar, PhD, PMP Senior Director, Global Regulatory Affairs and Clinical Safety Merck Sharp & Dohme Corp. (b) (6) [redacted]
OND Division / Office	Division of Antivirals (DAV)/Office of Infectious Diseases (OID)
Reviewer Name(s)/Discipline(s)	Clinical Reviewer: Aimee Hodowanec, MD Clinical Team Leader: Kimberly Struble, PharmD Clinical Virology Reviewer: Patrick Harrington, PhD Clinical Virology Team Leader: Jules O'Rear, PhD
Proprietary Name	Lagevrio
Established Name/Other names used during development	Molnupiravir (MK-4482; MOV; EIDD-2801)
Dosage Forms/Strengths	Oral capsule, 200 mg
Therapeutic Class	SARS-CoV-2 antiviral
Intended Use or Need for EUA	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19)
Intended Population(s)	Adults with a current diagnosis of mild-to-moderate COVID-19, who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Abbreviations: DAV, Division of Antivirals; EUA, emergency use authorization; OID, Office of Infectious Diseases; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1. Background

Molnupiravir (MOV, EIDD-2801) is a 5' isobutyrate prodrug of a cytidine ribonucleoside analogue, β-D-N^4-hydroxycytidine (NHC, EIDD-1931), which inhibits SARS-CoV-2 replication by viral mutagenesis. MOV received Emergency Use Authorization (EUA) on 12/23/2021 for "the treatment of adults with a current diagnosis of mild-to-moderate coronavirus disease 2019 (COVID-19) who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate" (Molnupiravir Fact Sheet for Healthcare Providers).

A recently released preprint (i.e., not peer-reviewed) manuscript by Sanderson et al., 2023, titled "Identification of a molnupiravir-associated mutational signature in SARS-CoV-2 sequencing databases," has led to some concerns in the scientific and non-scientific press about the potential for MOV to contribute to enhanced SARS-CoV-2 evolution that could result in emergence and spread of novel variants (e.g., Service 2023; Callaway 2023; Lowe 2023; Lauerman 2023).

On January 31, 2023, Drs. Janet Woodcock and Patrizia Cavazzoni received an email from Michael Lin, MD, PhD from Stanford University noting this Sanderson et al., 2023 preprint article as well as another recent publication by Butler et. al., 2022 regarding the PANORAMIC clinical trial and expressing several concerns regarding the MOV EUA:

- **Comment #1: The UK PANORAMIC trial, published in late December 2022 in The Lancet, showed no benefit of MOV in preventing severe disease in a high-risk population with prior immunity (not even a nonsignificant trend in favor of drug, really 0 benefit):**

  https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02597-1/fulltext

  As 95-100% of Americans now have prior immunity, this is the only study relevant to our current situation. The Phase 3 MOV trial showing 30% reduced risk of severe disease, which led to EUA, was in SARS2-immunonaive patients. UK NIHR press release at: https://www.nihr.ac.uk/news/molnupiravir-does-not-reduce-covid-19-hospitalisations-or-deaths-in-vaccinated-high-risk-people/32329

- **Comment #2: A survey of worldwide SARSCoV2 sequence databases showing widespread signatures of MOV-induced mutagenesis in patient samples, with some examples showing onward transmission:**

  https://www.medrxiv.org/content/10.1101/2023.01.26.23284998v2

  The expected pattern of MOV mutagenesis (increased G–>A mutations) was seen only after MOV approval and only in countries that approved it. Some mutant genomes with 31 mutations occurred in clusters, showing these mutated viruses are viable and can propagate. This mutation load is similar to that seen in Omicron BA.1 vs ancestral, which of course was associated

with enhanced transmission and increased immunoevasion. Thus it is possible for MOV to produce in a single round of infection a virus with enhanced propagative abilities; the more patients who take MOV, the higher the probability such an event would actually happen.

Following the release of the Sanderson et al., 2023 preprint and receipt of Dr. Lin's inquiry, DAV requested on February 2, 2023 that the Sponsor (i.e., Merck) provide an assessment on the findings reported in the Sanderson et al., 2023 article; the Sponsor submitted their assessment on February 9, 2023 in EUA 108 SDN 161.

This review memo includes the following:

- Summary of available MOV efficacy data, including recently published data from the U.K. PANORAMIC trial (Butler et al., 2022)
- DAV's Clinical Virology assessment of the Sanderson et al., 2023 preprint article
- Summary of the Sponsor's assessment of the Sanderson et al., 2023 preprint article
- High-level perspective on how on the findings from U.K. PANORAMIC trial (Butler et al., 2022) and the Sanderson et al., 2023 preprint article factor into the overall risk-benefit assessment of MOV

2. Review of Human Clinical Efficacy: Trial MK-4482-002 and PANORAMIC Trial

The data in support of the MOV EUA came from trial MK-4482-002 ("MOVe-OUT"), a randomized, double-blind, placebo-controlled, trial in patients with mild-to-moderate COVID-19. The Phase 3 (Part 2) portion of this trial was conducted from May 2021 through October 2021 and patients who had undergone SARS-CoV-2 vaccination were excluded. Overall, MOV was associated with a 3.0% (-5.9%, -0.1%) adjusted risk difference in hospitalization or death through Day 29 (nominal p-value = 0.0436). However, as described in detail in the EUA 108 12/23/2021 multi-disciplinary review, there was marked decrease in the molnupiravir treatment effect between the first and second half of the trial, that appeared to be driven by a decrease in the rate of hospitalization and death in the placebo arm over time, while rates of hospitalization and death remained relatively stable in the MOV arm.

Based on the observed reduction in the rate of hospitalization and death in the full MK-4482-002 Part 2 population, the review team concluded that the known and potential benefits of MOV outweigh the known and potential risks of MOV for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. However, given the modest benefit and the inconsistencies between the first and second half of trial MK-4482-002, MOV is only authorized for use for adults for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

More recently, MOV was studied in a large, randomized, controlled open-label, platform trial conducted in the UK, the PANORAMIC trial. The MOV portion of this trial was conducted from December 2021 to April 2022 and the trial enrolled a highly vaccinated patient population (98.9% had at least one dose of a SARS-CoV-2 vaccine and 94.4% had received at least three doses). This trial did not meet the pre-specified primary efficacy endpoint of hospitalization or death through Day 28 (103/12,516 [0.8%] in the MOV plus usual care group and 96/12,484 [0.8%] in the usual care group).

Molnupiravir did meet some of the secondary endpoints in PANORAMIC, including time to self-reported recovery [(9 days (range 5 to 23 days) in the MOV plus usual care group vs.15 days (range 7 days to not reached) in the usual care group]. However, the reliability of this symptom-based endpoint is uncertain, largely because of the trial's open-label design. (b) (4)

There are likely several factors that led to the low rates of hospitalization and death in the PANORAMIC trial. The PANORAMIC trial was conducted while the less virulent Omicron variant was circulating (whereas trial MK-4482-002 was conducted while the Delta variant was circulating). Further, in addition to enrolling a highly vaccinated population, the PANORAMIC trial also enrolled a less high-risk population. Individuals aged ≥ 50 years or aged 18-50 years with an underlying health conditions that made them "clinically vulnerable" were eligible for study participation. Approximately 17% of the study population consisted of persons aged 50-59 years without other risk factors for severe COVID-19. The patients at greatest risk for progression to severe COVID-19 had limited representation in the trial. For instance, <1% of study participants were transplant recipients. Further, patients at "very high risk" of severe COVID-19 (i.e., those with impaired immune systems or who are extremely clinically vulnerable) were eligible to receive monoclonal antibodies, intravenous antivirals (remdesivir), and oral antivirals (molnupiravir or nirmatrelvir–ritonavir) as "usual care."

Given the PANORAMIC trial design and study population, limited conclusions regarding the effectiveness of molnupiravir in treating mild-to-moderate COVID-19 can be drawn from this trial. Trial MK-4482-002 remains the primary source of data in support of the MOV EUA. (b) (4) . However, the results from MK-4482-002 are sufficient to fulfill the statutory requirements for an EUA (i.e., molnupiravir may be effective).

3. Overview of molnupiravir mechanism of action and impact on SARS-CoV-2 sequences and shedding

After oral administration, MOV is hydrolyzed by esterases to generate NHC, which circulates systemically. After cellular uptake, NHC is phosphorylated by host cell kinases to generate the active 5'-triphosphate, NHC-TP. The triphosphate acts as a

competitive alternative substrate by the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), nsp12, and the NHC-monophosphate (NHC-MP) is incorporated into negative- or positive-sense RNA in place of the monophosphates of C or U, which is attributed to the N4-hydroxycytosine base of NHC having two tautomeric forms allowing base pairing with either G or A. Over time, as NHC-MP is incorporated into viral RNA genomes and copied, changes accumulate in the viral genome, particularly G→A and C→U transition mutations, ultimately resulting in defective viral genomes. The mechanism of action of NHC as a viral RNA mutagen is well established and supported by data from several biochemical, cellular, and animal studies, as well as data showing increased numbers of nucleotide mutations in SARS-CoV-2 genome sequences from human participants treated with MOV in clinical trials (EUA 108 12/23/2021 multi-disciplinary review; EUA 000108 SDNs 98,100,101,104 clinical virology review).

As described in the EUA 108 reviews noted above, analyses conducted by FDA and the sponsor of SARS-CoV-2 sequences from MOV- and placebo-treated subjects in clinical trials showed higher frequencies of SARS-CoV-2 mutations in MOV-treated subjects. As an example, Table 1 (Merck Virology Report 07X2GY, pg. 88) shows an analysis conducted by Merck of nucleotide changes detected in SARS-CoV-2 sequences from subjects in the Phase 3 outpatient trial, MK-4482-002 Part 2 ("MOVe-OUT"). Consistent with the MOV mechanism of action, MOV treatment was primarily associated with elevated frequencies of transition mutations, i.e., G-to-A, C-to-U, A-to-G, and U-to-C mutations. Although less common, transversions and other (i.e., insertion/deletion) mutations also appeared to be enriched in MOV-treated subjects. It is unclear mechanistically how MOV would enrich for such changes, but this trend was also noted in the Phase 2 portion of the trial, MK-4482-002 Part 1.

Table 1. SARS-CoV-2 nucleotide mutations observed relative to baseline sequences in subjects enrolled in clinical trial MK-4482-002 Part 2 ("MOVe-OUT"). Source: Merck Virology Report 07X2GY.

			Transitions				Transversions								Other Nucleotide
Visit	Treatment	N	C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	Changes
EOT (Day 5)	MK-4482 800 mg	205	6.6	1.9	4.2	1.7	0.1	0.1	0.1	0.1	1.2	0.1	0.1	0.3	1.9
	Placebo	233	2.4	0.6	0.2	0.3	0.1	0.0	0.0	0.0	0.6	0.0	0.1	0.2	1.5
Day 10	MK-4482 800 mg	31	10.2	2.8	8.8	2.8	0.1	0.0	0.0	0.0	0.2	0.0	0.0	0.1	1.1
	Placebo	41	2.0	0.4	0.5	0.4	0.1	0.0	0.1	0.0	0.6	0.0	0.1	0.1	1.4
Day 15	MK-4482 800 mg	15	3.0	1.1	2.8	0.6	0.1	0.0	0.0	0.1	0.3	0.0	0.0	0.1	0.8
	Placebo	14	6.4	1.3	2.8	1.1	0.1	0.1	0.1	0.1	1.5	0.1	0.0	0.1	1.5
Day 29	MK-4482 800 mg	1	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0	2.0
	Placebo	4	8.0	1.8	2.0	0.8	0.0	0.0	0.0	0.3	2.3	0.0	0.3	0.3	3.3

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.
EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7.
Other Nucleotide Changes include insertions and deletions.

Viral genetic changes associated with MOV mutagenesis occur throughout the SARS-CoV-2 genome. Of particular interest, FDA and sponsor analyses of viral sequences from the MK-4482-002 Part 2 ("MOVe-OUT") trial identified a greater proportion of MOV-treated participants, compared to placebo-treated participants, had treatment-emergent amino acid substitutions detected in the viral spike (S) protein. Some of the S

substitutions had been associated with antibody escape and/or observed in major SARS-CoV-2 variants.

While these observations raise concerns that MOV could increase the rate of SARS-CoV-2 evolution and contribute to the generation of novel viral variants, it must also be recognized that MOV-associated mutagenicity more often leads to impairment of virus replication and reduced viral shedding, which likely reduces the chance that viruses bearing MOV-associated mutations are transmitted to other individuals. Studies directly investigating virus transmission from MOV-treated patients have not been conducted, but the impact of MOV on virus shedding was observed based on analyses of viral RNA and cell culture infectious virus obtained from NP swab samples from subjects in MK-4482-002 Part 2 ("MOVe-OUT"). As shown in Figure 1 (FDA analysis; EUA 000108 SDNs 98,100,101,104 clinical virology review), MOV treatment was associated with a modestly greater decline in SARS-CoV-2 RNA shedding through Day 5 (i.e., end-of-treatment). However, the impact of MOV on virus shedding is likely better reflected by analyses of cell culture infectious virus. While the detection of cell culture infectious SARS-CoV-2 quickly declined in both MOV and placebo-treated subjects, a more pronounced decline was seen in MOV-treated subjects (Table 2, FDA analysis; EUA 000108 SDNs 98,100,101,104 clinical virology review). The cell culture assay provides a readout of MOV antiviral activity that is arguably more relevant to the mutagenic mechanism of MOV, as MOV is likely to exert an effect on viral infectivity and replication fitness prior to an effect on overall viral RNA levels. Of note, 4 of the MOV-treated subjects were immunocompromised and had culturable virus detected at baseline; no virus could be isolated from these subjects at any timepoint after initiation of MOV.

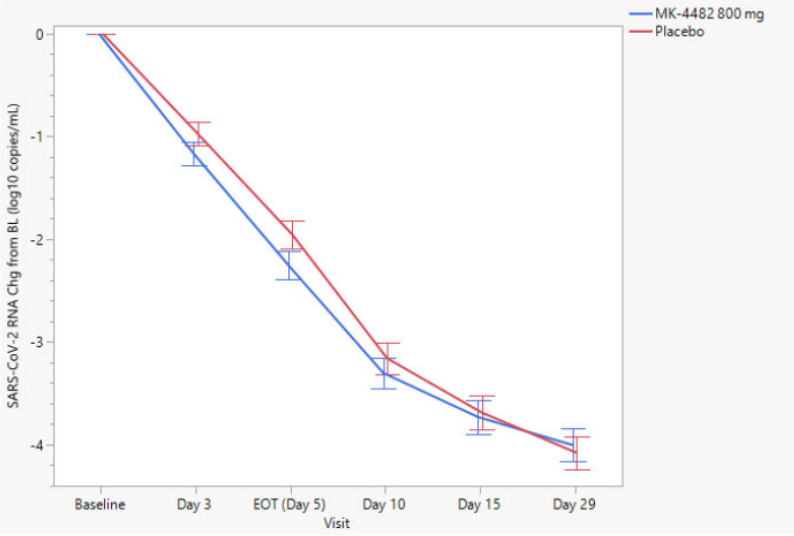

Figure 1. Change in SARS-CoV-2 RNA levels in NP samples from MK-4482-002, Part 2. Results show mean values and 95% confidence intervals. MK-4482, molnupiravir. Source: FDA analysis.

Table 2. Detection of cell culture infectious SARS-CoV-2 in MK-4482-002, Part 2. Analyses were conducted only for those with baseline and post-baseline results. IA, interim analysis.

	All Subjects		Subjects with Positive Infectivity Result at Baseline	
	MOV 800 mg BID	Placebo	MOV 800 mg BID	Placebo
Baseline	14.3% (96/671)	14.5% (97/670)	100.0% (96/96)	100.0% (97/97)
Day 3	0.5% (3/637)	4.7% (30/643)	0.0% (0/92)[1]	20.8% (20/96)[2]
EOT (Day 5)	0.0% (0/623)	1.0% (6/616)	0.0% (0/91)	2.2% (2/89)[3]
Day 10	0.2% (1/583)	0.2% (1/582)	0.0% (0/82)	0.0% (0/86)
Day 15	0.0% (0/581)	0.0% (0/580)	0.0% (0/78)	0.0% (0/83)
Day 29	0.0% (0/577)	0.0% (0/590)	0.0% (0/77)	0.0% (0/89)

[1]All 92 negative results in subgroup were observed, not imputed. [2]15/69 in IA population, 5/27 in Post-IA population. [3]2/67 in IA population, 0/22 in Post-IA population.

As noted above, to our knowledge, clinical studies directly investigating transmission of SARS-CoV-2 from MOV-treated patients have not been conducted to assess and quantify the risk of transmission of MOV-mutagenized viruses to others. However, studies conducted in a ferret model of SARS-CoV-2 infection showed early MOV treatment was associated with reduced virus shedding and impairment of virus transmission to contact ferrets (Cox et al., 2020; Lieber et al., 2022).

4. Summary of Sanderson et al., 2023 preprint publication

The referenced preprint manuscript identified a possible correlation between MOV availability and SARS-CoV-2 sequences/sequence clusters with mutational signatures claimed to be consistent with MOV-mediated mutagenesis, but a causal relationship has not yet been established.

In analyses of published SARS-CoV-2 sequences from the GISAID database, the authors identified viral sequences with long phylogenetic branches that contained what they viewed as higher-than-expected numbers of G-to-A mutations, and the authors hypothesized these sequences represent a mutational signature of MOV-mediated mutagenesis consistent with MOV-associated mutation patterns observed in the AGILE clinical trial.

These high G-to-A containing, long phylogenetic branches in the GISAID database were almost exclusively detected in sequences submitted in 2022, after the introduction of MOV in the U.S. and several other countries (Figure 2; from Sanderson et al., 2023). Furthermore, these branches appeared to be most common in the U.S., Australia and the U.K., where MOV is authorized, and less common in certain countries where MOV is not authorized, such as Canada and France. Considering viral sequences from the U.S. and Australia, the branches were also identified more commonly in sequences from older individuals, which the authors claimed was consistent with a “prioritized” use of MOV to treat older individuals. The authors also identified some examples of long SARS-CoV-2 phylogenetic branches with high numbers of G-to-A and other transition mutations that appeared to give rise to descendant sequences, leading the authors to

speculate that viruses with MOV-associated signature mutations were transmitted to others.

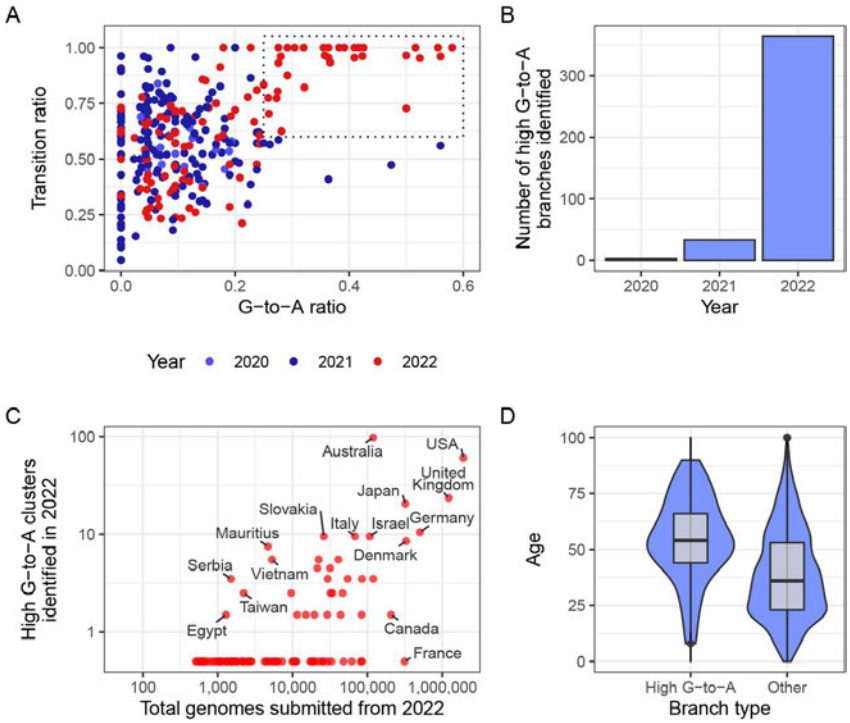

Figure 2. Identification of SARS-CoV-2 sequences in GISAID database with long branch lengths and high concentrations of G-to-A mutations. Source: preprint publication by Sanderson et al., 2023.

While it is plausible that MOV use could contribute to mutational patterns in SARS-CoV-2 sequences, there are some uncertainties regarding the authors claims and the public health implications of their results, including the following:

- Because the viral sequence data do not include information on the timing of virus sampling and whether the patients were even treated with MOV or any other agent, none of these findings can be directly attributed to MOV use. Therefore, the authors claim that these high G-to-A mutation, long phylogenetic branches are associated with MOV use is entirely hypothetical.
- The authors claim that the high G-to-A mutation, long phylogenetic branches primarily arose in 2022 following the introduction of MOV in the U.S. and several other countries (Fig. 1B). However, the numbers presented in this analysis are absolute numbers, and the denominators for the numbers of sequences analyzed were not reported so it is not possible to determine if this represents an increase in the frequencies of sequences with high G-to-A mutation, long phylogenetic branches, or if this can be attributed at least in part to an increasing number of viral sequences available for analysis.
- The high G-to-A mutation sequences identified by the authors represent a small fraction of the total genomes submitted to GISAID in 2022. For example, Australia had the highest numbers of such sequences but this reflected 0.08%

(97/119,194) of sequences. In the U.S., this frequency was 0.003% (60/1,911,997), and in the U.K., the country where MOV was first approved (Syed, 2022) the frequency was 0.002% (23/1,218,724). Thus, even if these sequences can be attributed directly to MOV mutagenesis, they do not contribute a substantial proportion of SARS-CoV-2 sequences in the GISAID database in 2022.

- It should also be noted that in the absence of MOV or any other antiviral agent, mutations arise throughout the SARS-CoV-2 genome through natural viral replication, and that transition mutations in general are more frequently introduced during replication than other types of changes (transversion mutations [i.e., purine↔pyrimidine], insertions, and deletions). Therefore, it is challenging to assert a precise "signature" mutational pattern to MOV use when it does not create novel mutations, but rather increases the frequencies of mutations that are already generated naturally.
- Long phylogenetic branches can also be a result of inconsistent SARS-CoV-2 genetic sampling in a particular sub-population. This could lead to collection of some genetically distant viral sequences without representation of other phylogenetically related sequences with intermediate numbers of mutations that were present in the population but were not adequately sampled.
- Technical issues could contribute to artifactual variability in mutational patterns in the database sequences, such as the specific next generation sequencing assay platform/chemistry, variability in clinical sampling and processing, and variability in viral RNA concentrations in clinical specimens (e.g., low viral RNA concentrations could contribute to a higher rate of mutations detected).

5. Sponsor's assessment of Sanderson et al., 2023 preprint publication

The sponsor has reviewed the preprint publication and noted that there are "gaps in the analyses done by the authors to draw their conclusions." Some of the concerns and uncertainties highlighted by the sponsor are the same as those independently identified in DAV's review of the article. Specific points raised in the sponsor's assessment include the following (paraphrased):

- The authors assume that the observed SARS-CoV-2 mutations are associated with MOV treatment, relying on circumstantial associations between viral sequence origin and timeframe of sequence collection in countries where MOV is available, with no direct evidence that the viral sequences arose from MOV use.
- In the analyses of high G-to-A, long phylogenetic branch sequences by year, the authors did not normalize the number of long branches identified to the total number of sequences analyzed each year. It is possible that an increase in high G-to-A, long branch sequences was a function of the increased number of sequences analyzed in 2022. This is supported by the plot of the number of high G-to-A branches identified by the total number of sequences submitted by

country (referring to Figure 2C above), showing that the number of high G-to-A branches generally increases with greater number of available sequences.

- Given that high G-to-A branches represent only approximately 4.5% of the total long branches observed, similar analyses should have been conducted to evaluate other types of transitions (e.g., T-to-C and A-to-G) and other types of mutations (e.g., G-to-T) to determine whether these patterns were also observed during the evaluation period.
- The authors do not consider alternative scenarios for the existence of long phylogenetic branches, such as gaps in the database due to unavailability of intermediate genomes at the time of analysis. For example, sparse sampling, delays in sequencing, or data submission to the GISAID database, could all contribute to an incomplete phylogenetic tree, resulting in generation of sporadic long branch arms.
- In India, a country where generic versions of MOV are available, only 3 high G-to-A branches were identified, despite having a similar number of submitted sequences as Australia.
- The noted genetic mutations can also occur as a result of normal viral evolution. Of the 25 mutations identified in the Australian cohort, all 25 have been previously observed in SARS-CoV-2 genomes isolated prior to the authorization of MOV, confirming that all individual errors attributed to MOV use in this example occur through normal viral evolution.
- The authors describe a single sequence containing over 130 mutations and speculate, without evidence, that this highly mutated virus may have arisen as a result of multiple courses of MOV treatment in a chronically infected individual. Administration of multiple courses of MOV should be an uncommon clinical scenario as chronic infection with SARS-CoV-2 is rare, and treatment with MOV for longer than 5 days would not be consistent with prescribing information.
- Statistical analyses of the of data to support the author's conclusions are not provided.
- Data from clinical trials have demonstrated that MOV use results in a rapid decline in viral infectivity. The authors acknowledge that the mutations are likely deleterious or neutral, in which case the virus would likely become less fit.
- There is no known impact of MOV-associated transition mutations on MOV resistance or transmission of novel variants of concern.

6. Review Team's Perspectives and Conclusions

- The data available regarding efficacy in the Omicron era and in vaccinated individuals are limited for all approved and authorized SARS-CoV-2 antivirals. This is not unique to MOV. High rates of SARS-CoV-2 seropositivity (from vaccination or natural infection) combined with the predominance of the less

virulent Omicron variant make it more difficult to show an effect on hospitalization and death given the low background rate of these outcomes.

- MOV was not shown to be associated with a reduction in the rate of hospitalization or death in the PANORAMIC trial. We believe that this is largely attributable to the enrollment of a less high-risk population, as evidenced by a hospitalization/death rate of < 2% in both the molnupiravir arm and the usual care arm.

- MOV was associated with a modest decrease in hospitalization and death in the Phase 3 trial, MK-4482-002. This "modest efficacy" is accounted for in the second-line authorized use statement, whereby MOV is only authorized for use in patients for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

- While a large portion of the U.S. population has now been previously infected with SARS-CoV-2 and/or vaccinated against COVID-19, the most immunosuppressed patients may not have developed effective immunity following infection and/or vaccination. These patients may be closer to the "immunonaive" MK-4482-002 study population than the PANORAMIC study population.

- Now that EVUSHELD is no longer an effective means of preventing COVID-19 in the most vulnerable patients, the availability of multiple effective antiviral treatments is more important than ever. Many of these highly immunosuppressed patients also take concomitant medications that prevent them from being able to safely take PAXLOVID.

- The Sanderson et al., 2023 preprint manuscript identified a possible correlation between MOV availability and SARS-CoV-2 sequences/sequence clusters with mutational signatures claimed to be consistent with MOV-mediated mutagenesis. While it is plausible that MOV use could contribute to mutational patterns in SARS-CoV-2 sequences, there are some uncertainties regarding the authors claims and the public health implications of their results, and a causal relationship between MOV use and the noted SARS-CoV-2 sequence patterns has not yet been established.

- The potential for MOV-induced mutations to affect SARS-CoV-2 evolution was acknowledged prior to the EUA for MOV, and this concern was addressed in the EUA 108 12/23/2021 multi-disciplinary review and discussed at the November 30, 2021 Advisory Committee meeting on the EUA for MOV (meeting transcript).

- Nonclinical and clinical virology studies have shown that MOV-associated mutagenicity leads to impairment of virus replication and reduced viral shedding, which is expected to reduce the risk of transmission of viruses bearing MOV-associated mutations to other individuals.

- The theoretical potential for an antiviral agent to contribute to SARS-CoV-2 evolution is not unique to MOV. The selective evolutionary pressures conferred by other agents, including small molecule antiviral drugs and virus Spike protein-targeting monoclonal antibodies, can contribute to the emergence or enrichment of SARS-CoV-2 variants with reduced susceptibilities to these agents.

- The preprint publication by Sanderson et al., 2023 does not change the review team's overall risk assessment of MOV. The risk that MOV use could contribute to SARS-CoV-2 genetic changes that are transmissible remains challenging to quantify, and DAV will continue to closely monitor the scientific literature for related preprints and published papers. We also look forward to the broader scientific community's assessment of this work. Ultimately, any risk of MOV-associated SARS-CoV-2 mutagenicity must be considered in the context of other risks and benefits of MOV.

- The evidentiary standard for an EUA is different than that for an NDA. The criteria for issuing an EUA include a requirement that it be reasonable to believe that the product *may be* effective in treating a serious or life-threatening disease. We continue to believe that molnupiravir meets this requirement. Further, it is the review team's current position that the risk-benefit assessment of MOV as a second-line therapy remains acceptable. We will continue evaluating data, including new real world data and any clinical trial data as they become available, noting the many limitations of real world data.

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