

**DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW**

EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

Reviewers: Patrick R. Harrington, Ph.D.
Aimee Hodowanec, M.D.

Assigned/Reviewed SDNs:

SDNs	eCTD#	Rec'd Date	Assign Date	Content
112	0110	5/6/2022	5/6/2022	Response to 4/25/2022 request for analyses of SARS-CoV-2 rebound or reinfections following molnupiravir treatment
121	0120	7/26/2022	7/27/2022	Response to 7/18/2022 communication regarding proposed HCP fact sheet edits and request for confirmation of FDA analyses of viral RNA rebound from study MK-4482-002 Part 2.
126	0124	7/29/2022	7/29/2022	Response to 7/28/2022 communication regarding proposed HCP fact sheet edits. Sponsor accepts all fact sheet revisions.

Sponsor:

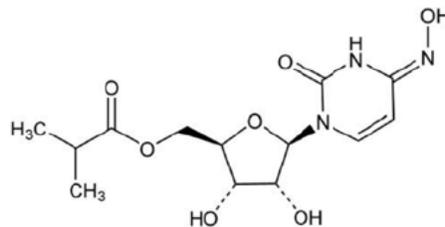
SEE ATTACHED ADDENDUM

Sushma Kumar, Ph.D., PMP, Director, Global Regulatory Affairs

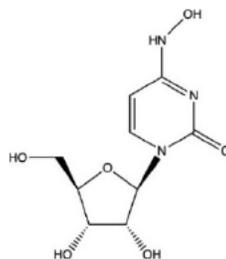
Product Names: Molnupiravir (MOV, MK-4482, EIDD-2801; 5'-isobutyrate prodrug of EIDD-1931 [β -D-N⁴-hydroxycytidine, NHC]); LAGEVRIO™

Chemical Names: (2R, 3S, 4R, 5R)-3, 4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3, 4-dihydropyrimidin-1(2H)-yl] oxolan-2-yl) methyl 2-methylpropanoate

Structure:



MOLNUPIRAVIR (prodrug)



NHC (nucleoside analogue)

Molecular Formula: C₁₃H₁₉N₃O₇

Molecular Weight: 329.31 (MOV); 259.22 (nucleoside analogue)

Drug Category: Antiviral

EUA Indication: Treatment of mild to moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 and/or hospitalization.

Dosage Form/Route of administration: 200 mg capsules/oral

Abbreviations: CoV, coronavirus; EOT, end of treatment; LLOQ, lower limit of quantification; MOV, molnupiravir; NHC, β -D-N⁴-hydroxycytidine; NP, nasopharyngeal; nsp, nonstructural protein; PFU, plaque forming units; SARS, severe acute respiratory syndrome;

DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

BACKGROUND

Molnupiravir (MOV, EIDD-2801) is a 5' isobutyrate prodrug of a cytidine ribonucleoside analogue, β -D-N⁴-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 mild-to-moderate coronavirus disease 2019 (COVID-19) in adults with positive results of direct 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 approved or authorized by FDA are not accessible or clinically appropriate” ([Molnupiravir Fact Sheet for Healthcare Providers](#)).

This set of submissions includes the sponsor’s response to a DAV [4/25/2022](#) request that the sponsor provide a summary from clinical trials (molnupiravir and placebo arms), global safety databases and any real-world data of patients reporting potential symptomatic SARS-CoV-2 rebound or reinfections soon after concluding MOV treatment (SDN 112). In addition, in SDN 121 the sponsor provided a response to a DAV [7/18/2022](#) communication that included (1) proposed new text for the LAGEVRIO EUA Fact Sheet for Healthcare Providers, and (2) a request for the sponsor to confirm independent FDA analyses of viral RNA rebound in the MK-4482-002 Part 2 (MOVE-OUT) trial.

In late April 2022, the Division became aware of case reports and stories in the press and social media related to patients who experienced symptomatic recovery during PAXLOVID (nirmatrelvir/ritonavir, EUA 000105) treatment, but after stopping the 5-day course of treatment experienced “relapses” in COVID-19 symptoms which were coincident with rebounds in qualitative or quantitative viral RNA, antigen or virus detection in upper respiratory tract samples (e.g., see [Gupta et al., 2022](#); [Charness et al., 2022](#); [Carlin et al., 2022](#); [Washington Post 4/27/2022 article](#)). These cases have occurred in immunocompetent, vaccinated individuals, indicating that the phenomenon is not attributed to immune deficiency. Furthermore, there has been no reported evidence that these cases are related to emergence of nirmatrelvir-resistant virus. These reports have raised concerns and some speculation that PAXLOVID treatment, or perhaps other short duration, small molecule antiviral treatments like molnupiravir, may suppress virus replication in a manner that delays the development of a functional host immune response that is ultimately responsible for clearing the infection, and that a longer treatment duration or re-treatment of “relapse” cases may be needed for optimal efficacy and to minimize the risk of SARS-CoV-2 transmission from treated individuals.

As described in SDN 112 (see [SDN 112 Response Document](#)) the sponsor reviewed data from the Phase 3 clinical trial, MK-4482-002 (P002), Part 2, as well as the company global safety database, to identify patients having a rebound in clinical symptoms and SARS-CoV-2 detection after completing COVID-19 treatment. The sponsor noted that no “real-world” data were available at the time.

This review summarizes post-hoc analyses conducted by the sponsor, and additional analyses independently conducted by FDA, to investigate the frequency, role of MOV treatment, and the potential clinical relevance of post-treatment SARS-CoV-2 RNA rebound using available virology, genotypic resistance and clinical data from the Phase 3 trial, MK-4482-002 (P002), Part 2. As noted above, the sponsor also investigated this topic using their internal global safety database.

In addition, this review serves to document the rationale for updates made to the Approved Available Alternatives section of the Lagevrio™ EUA Fact Sheet for Healthcare Providers.

DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

SPONSOR’S ANALYSES OF POST-TREATMENT SARS-COV-2/COVID-19 REBOUND

MK-4482-002 (P002), Part 2

MK-4482-002 (P002), Part 2, was a Phase 3, randomized, placebo-controlled, double-blind trial evaluating the efficacy, safety and PK of MOV administered to non-hospitalized subjects ≥18 years of age with RT-PCR-confirmed COVID-19. MOV was dosed at 800 mg q12h for 5 days, and the primary clinical efficacy endpoint was the rate of hospitalization or death through Day 29.

SARS-CoV-2 RNA levels in nasopharyngeal (NP) swab samples were analyzed at baseline, Day 3, End of Treatment (EOT; Day 5), Day 10, Day 15, and Day 29. A research-use-only quantitative SARS-CoV-2 assay developed at Q2-solutions (Morrisville, NC, USA) was used to measure the viral RNA levels. The sponsor defined viral RNA rebound as a “negative” quantitative SARS-CoV-2 RNA result, which reflects results below the assay lower limit of quantification (LLOQ=500 copies/mL) obtained at Day 5 (EOT) or later, which is then followed by a result that is a >1 log₁₀ increase from this negative result (i.e., ≥5,000 copies/mL) at a later visit.

To identify participants with viral RNA rebound associated with at least one clinical symptom, data collected from a 15-item daily paper COVID-19 symptom diary completed by participants were reviewed in participants identified to have viral RNA rebound according to the definition above. These participants were identified as having 1) viral RNA rebound and 2) relapse and/or progression (defined below) of at least 1 sign or symptom or hospitalization occurring within (+/-) 1 visit relative to the visit in which the viral RNA rebound occurred (e.g., a participant with viral RNA rebound on Day 15, and with relapse and/or progression of COVID-19 symptoms or hospitalization that are reported from the Day 10 visit through the Day 29 visit would be considered to have met the definition). The visit windows were defined as shown in Table 1 ([SDN 112 Response Document](#), pg. 2).

Table 1. Analysis visit windows (MK-4482-002 supplementary statistical analysis plan, 11/12/21).

Study Period	Visit	Target Day	Analysis Day Range (Relative to Randomization)
Screening	Baseline	Screening	Prior to first dose
Intervention	Day 3	Day 3	Day 2 - Day 4 and after first dose
	EOT (Day 5) ^a	Day 5	Day 5 - Day 7
Follow-up	Day 10	Day 10	Day 8 - Day 12
	Day 15	Day 15	Day 13 - Day 22
	Day 29	Day 29	Day 28 - Day 35
	LFU	Month 7	

^a EOT (Day 5) includes post-baseline records from day 5 (relative to randomization) up to day 7. End of treatment visits occurring earlier than day 5 (relative to randomization) are included in the Day 3 visit.

Definitions of sign/symptom relapse and progression used for this summary are based on the definitions outlined in the protocol (MK-4482-002-04, Section 9.4.1.1). Relapse is defined as the first of 2 or more consecutive days of each self-reported sign/symptom returning to the baseline severity or worse than baseline severity after the criteria for sustained resolution or improvement are met (defined as the number of days from randomization to the first of 3 consecutive days when resolution or improvement is demonstrated for each targeted self-reported sign/symptom). Progression is defined as the first of 2 consecutive days when the self-reported sign/symptom worsens compared with baseline, or was not present at baseline but subsequently developed post-baseline. In addition to participants

**DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW**

EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

with symptomatic relapse and/or progression, any participant with viral RNA rebound and who was hospitalized after the EOT visit was also included since not all hospitalized participants completed the symptom diary following hospitalization. Finally, only participants who had a baseline quantitative SARS-CoV-2 RNA result above the LLOQ (i.e., ≥ 500 copies/mL) and who completed the full course (i.e., 10 doses) of study intervention were evaluated for potential symptomatic viral rebound. A total of 1153 participants were randomized and received a full course of study intervention, AND had a baseline SARS-CoV-2 RNA result \geq LLOQ (587 in the MOV group, and 566 in the placebo group).

Based on the criteria outlined above, a total of 14 participants were identified (8/587 [1.4%] in the MOV group, and 6/566 [1.1%] in the placebo group) with symptomatic viral rebound. Key participant characteristics are summarized in Table 2 ([SDN 112 Response Document](#), pgs. 4-5), and were considered generally similar between treatment groups. No participants had cell culture infectious virus detected in NP swabs collected at any post-baseline visit, and none of these participants had been hospitalized.

Table 2. Individual subjects in MK-4482-002 (P002), Part 2 identified by sponsor with post-treatment rebound in viral RNA and symptom rebound.

Participant	Sex	Age	TSSO (days)	IC Status (Yes/No)	Anti-N AB Status	Anti-Spike nAB Status	Variant Clade	Baseline VL ^a	Timing of 1 st Result Below LoQ	Visit of Viral Rebound/ VL ^a	Symptoms Relapsed (R) or Progressed (P)	Hospitalization Status (Yes/No)	Infectivity Results at Time of Viral Rebound ^b
MOV													
(b) (6)	F	49	>3	No	Negative	Negative	19B (Washington State)	6.75	Day 15	Day 29 / 3.81	Feeling Hot or Feverish (R) Chills (P)	No	Negative
	M	48	≤ 3	No	Negative	Negative	21J (Delta)	10.21	Day 10	Day 15 / 4.98	Fatigue (R) Cough (P)	No	Negative
	M	65	≤ 3	No	Negative	Positive	21J (Delta)	5.72	Day 3	Day 29 / 5.46	Fatigue (R)	No	Negative
	F	46	>3	No	Negative	Negative	21J (Delta)	5.31	Day 10	Day 15 / 4.27	Sore Throat (R)	No	Negative
	M	35	>3	No	Negative	Negative	21J (Delta)	8.41	Day 10	Day 15 / 5.14	Headache (R) Shortness of Breath or Difficulty Breathing (P)	No	Negative
	M	50	≤ 3	No	Negative	Negative	21I (Delta)	7.92	Day 15	Day 29 / 5.32	Runny Nose (R) Diarrhea (P) Sore throat (P)	No	Negative
	F	23	>3	No	Negative	Negative	21J (Delta)	6.06	EOT	Day 10 / 4.29	Muscle or body aches (R) Fatigue (R) Shortness of breath (P)	No	Negative
	M	47	≤ 3	No	Negative	Negative	21J (Delta)	6.75	Day 15	Day 29 / 3.99	Headache (P)	No	Negative

**DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022**

Table 2 continued. Individual subjects in MK-4482-002 (P002), Part 2 identified by sponsor with post-treatment rebound in viral RNA and symptom rebound.

Participant	Sex	Age	TSSO (days)	IC Status (Yes/No)	Anti-N AB Status	Anti-Spike nAB Status	Variant Clade	Baseline VL ^a	Timing of 1 st Result Below LoQ	Visit of Viral Rebound/ VL ^a	Symptoms Relapsed (R) or Progressed (P)	Hospitalization Status (Yes/No)	Infectivity Results at Time of Viral Rebound ^b
Placebo													
(b) (6)	M	38	≤3	No	Negative	Negative	20J (Gamma)	8.94	Day 10	Day 15 / 4.68	Chills (R) Loss of Taste (R) Sore Throat (P)	No	Negative
	F	31	>3	No	Negative	Negative	21H (Mu)	7.14	EOT	Day 10 / 5.00	Muscle or body aches (R)	No	Negative
	M	28	>3	No	Negative	Negative	20I (Alpha)	6.40	Day 10	Day 15 / 3.73	Sore throat (R) Headache (R) Muscle or Body Aches (R) Runny Nose (R) Diarrhea (P)	No	Negative
	F	68	>3	No	Negative	Negative	Unknown	7.39	EOT	Day 10 / 3.87	Feeling Hot or Feverish (P) Headache (P) Loss of Smell (P) Loss of Taste (P) Shortness of Breath or Difficulty Breathing (P)	No	Negative
	M	54	>3	No	Negative	Negative	21J (Delta)	7.87	Day 10	Day 15 / 3.88	Shortness of Breath or Difficulty Breathing (P)	No	Negative
	M	25	>3	No	Positive	Negative	21J (Delta)	6.90	Day 10	Day 15 / 4.05	Cough (R) Runny Nose (P)	No	Negative
MOV=molnupiravir; IC=immunocompromised; TSSO=time from symptom onset; anti-N AB=anti-nucleocapsid antibody; nAB=neutralizing antibody; LoQ=limit of quantification; VL=viral load. ^a log ₁₀ copies/milliliter (mL) ^b Infectivity results are imputed as undetectable if the sample was not sent for infectivity testing due to SARS-CoV-2 RNA titer being lower than 10 ⁵ copies/mL.													

Analysis of Company Global Safety Database

The Company's global safety database was searched for valid reports for any of the following Preferred Terms: 'COVID-19', 'SARS-CoV-2 test positive', 'disease recurrence', and 'drug ineffective' that were received from spontaneous and noninterventional sources as of 26-Apr-2022. In addition, the same search was conducted in the Eudravigilance (EVDAS) database. Spontaneous and non-interventional data sources include reports from EUA, unregistered product supply (UPS), early access programs, non-Company sponsored studies, healthcare professionals, consumers, competent authorities (worldwide), and scientific literature for MOV. The safety database includes valid social media reports (i.e., reports with a contactable reporter, identifiable AE and a Merck product). As of 26-Apr-2022, the global safety database contained approximately 2500 spontaneous and non-interventional case reports received from about 25 countries.

The search of the Company's global safety database yielded a total of 123 cases that included at least one of the above Preferred Terms. No additional cases were identified from EVDAS. All 123 case narratives were reviewed to identify reports of: (1) patients who completed MOV therapy with improvement/resolution of symptoms followed by recurrence of symptoms with or without a reported repeat SARS-CoV-2 test; and (2) patients who had a negative SARS-CoV-2 test after completing MOV therapy followed by a positive test. Reports of patients not completing a full course of MOV therapy for any reason were excluded. Reports of patients who had no improvement or disease worsening at the end of therapy, and reports that only reported 'drug ineffective' without additional details were also excluded. A total of 5 cases satisfied one or both criteria (3 satisfied both criteria, 2 satisfied criterion 1). In addition, 3 cases did not fully satisfy either criterion as the cases did not describe resolution of symptoms at the end of MOV therapy; however, these 3 cases are included as a possible recurrence

DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

because the reporter mentioned COVID-19 reinfection or mentioned COVID-19 symptoms only in association with the second test.

Of the total 8 cases, 3 were reported from Germany and 5 from Japan. Age of patients ranged between 45 years and 95 years, with 7 cases in patients ≥ 75 years of age. Gender was reported for 7 cases, 4 females and 3 males. Medical history was reported in 4 cases [hypertension (1), hepatic cancer (1), dementia (1) and bronchial asthma and dementia (1)]. Time to onset of recurrent symptoms after the end of MOV therapy was reported in 5 cases and ranged between 1 day to 10 days. The outcome of the events was reported in 4 cases: 2 recovered (with 1 of the 2 hospitalized upon family request due to underlying dementia), 2 hospitalized (1 treated with sotrovimab and was reported as recovered, and 1 reported as the cause of hospitalization to be unclear if due to COVID-19). History of receipt of a COVID-19 vaccine was reported in 1 out of 8 cases.

The sponsor concluded that overall, these few cases lacked crucial details for evaluation such as initial COVID-19 symptoms or the symptoms that occurred after the completion of MOV therapy, exact start/stop dates of MOV therapy, underlying comorbidities, concurrent medications and virology testing. Details of the 8 cases are included in the [SDN 112 Response Document](#) (pgs. 7-10).

INDEPENDENT FDA ANALYSES OF VIRAL RNA REBOUND IN STUDY MK-4482-002 PART 2

Identification of Subjects with Post-treatment SARS-CoV-2 RNA Rebound

Viral RNA data reported from Study MK-44482-002 Part 2 were independently analyzed to characterize the frequency and potential clinical relevance of rebounds in viral RNA levels following treatment with MOV or placebo. These analyses used the [ADRNA](#) dataset reported in SDN 98. Viral RNA results were available from 1,406 subjects in the modified intent-to-treat (mITT) population, defined as all randomized participants who received at least 1 dose of study intervention and were not hospitalized before the first dose of study intervention.

Consistent with previously documented analyses ([EUA000108.000](#); [EUA 000108 SDNs 98-104](#)), treatment with MOV was, on average, associated with a modestly more rapid decline in viral RNA levels compared to placebo, with a $\sim 0.3 \log_{10}$ copies/mL greater mean decline in viral RNA levels through Day 5/EOT (Figure 1-top, FDA analysis). However, it should be noted that there was substantial inter- and intra-subject variability in viral RNA levels over time, with evidence of fluctuations in viral RNA levels for individual subjects throughout the study period (Figure 1-bottom, FDA analysis).

**DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW**
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

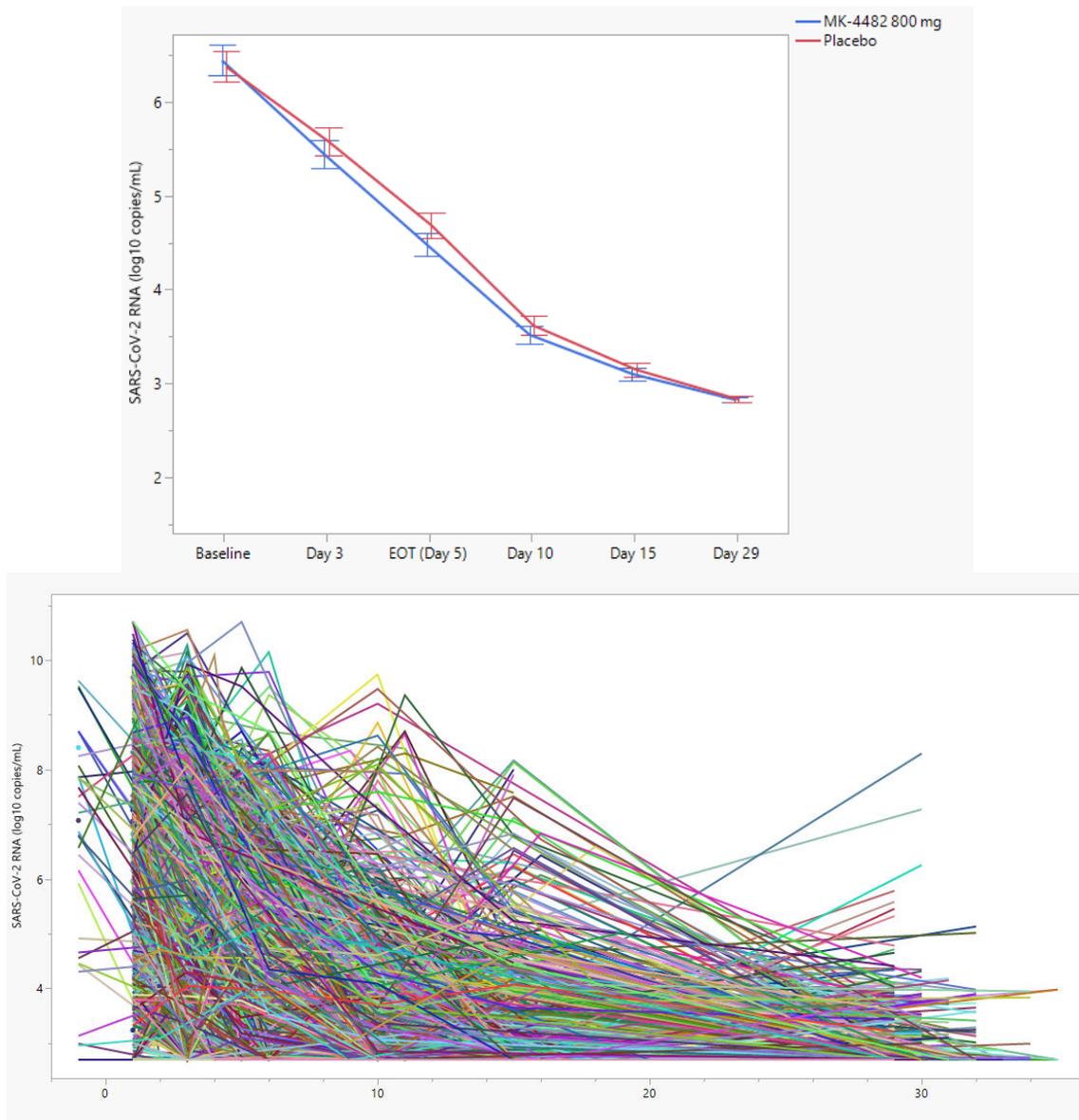


Figure 1. Mean (\pm 95% confidence interval) SARS-CoV-2 RNA levels in NP swab samples according to analysis visit window (top), and results for individual subjects by Study Day.

Comment (internal): This reviewer had previously calculated a ~ 0.2 log₁₀ copies/mL greater mean decline in viral RNA levels through Day 5/EOT for MOV versus Placebo recipients, but this appears to be a minor analysis or rounding error, and in the [SDN 121 Response Document](#) the sponsor correctly noted that the difference was ~ 0.3 log₁₀ copies/mL.

The following set of criteria was used as a sensitive measure to identify subjects with any evidence of post-treatment viral RNA rebound:

Day 10/15/29 (LLOQ/0.5 Combined): Any evidence of viral RNA rebound from Day 5 to Day 10, 15 or 29, based on (a) RNA $<$ LLOQ at Day 5 and \geq LLOQ on Day 10, 15 or 29, or (b) RNA \geq LLOQ on Day 5 and 0.5 log₁₀ copies/mL increase from Day 5 on Day 10, 15 or 29.

**DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW**

EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

This definition is similar to the sensitive definition used for analyses of viral RNA rebound in the PAXLOVID C4671005 (EPIC-HR) trial (EUA 000105), except that the MK-44482-002 Part 2 trial included a virologic assessment on Day ~29, while the latest planned virologic assessment for the PAXLOVID C4671005 trial occurred on Day ~14. The denominator for the calculated rate of viral RNA rebound was based on subjects who had a Day 5/EOT viral RNA result and at least one viral RNA measure on Day 10, 15 or 29.

Based on these criteria, post-treatment viral RNA rebound was observed in 10.8% (68/627) of MOV recipients, and 10.3% (64/623) of placebo recipients ($p=0.8$, Fisher's Exact test) (Figure 2, FDA analysis).

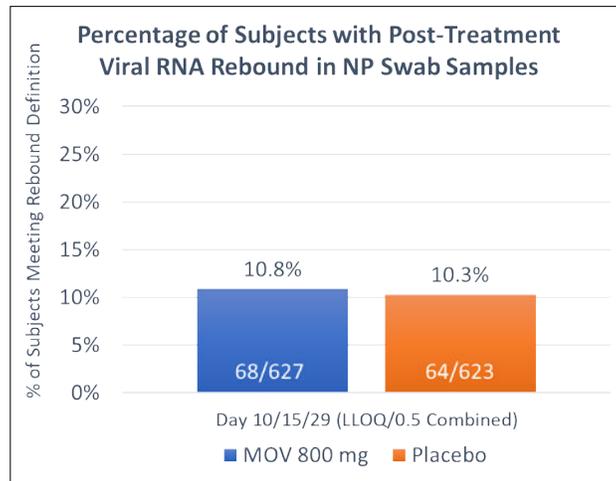


Figure 2. Proportion of subjects with evidence of post-treatment SARS-CoV-2 RNA rebound in NP samples in MK-44482-002 Part 2.

Viral RNA levels for individual subjects with post-treatment viral RNA rebound (Day 10/15/29 [LLOQ/0.5 Combined] definition) are shown in Figure 3 (FDA analysis). The patterns of viral RNA rebound were variable across different subjects, and did not obviously differ between MOV recipients and placebo recipients.

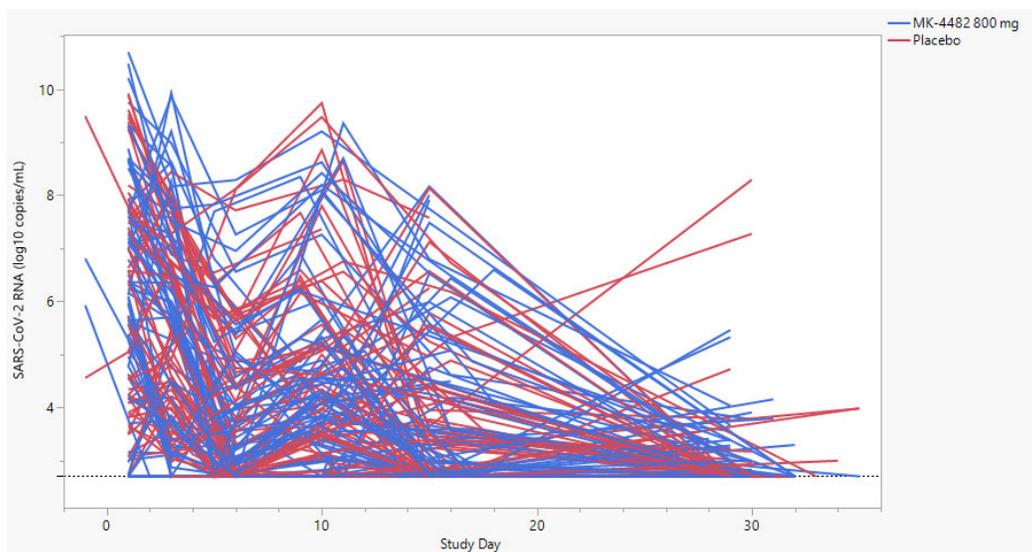


Figure 3. Viral RNA levels in NP samples for individual subjects with evidence of post-treatment SARS-CoV-2 RNA rebound in MK-44482-002 Part 2.

DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

Observations of rebound occurred on Day 10, Day 15 and Day 29, although most cases occurred first by Day 10 or Day 15 (Figure 4, FDA analysis).

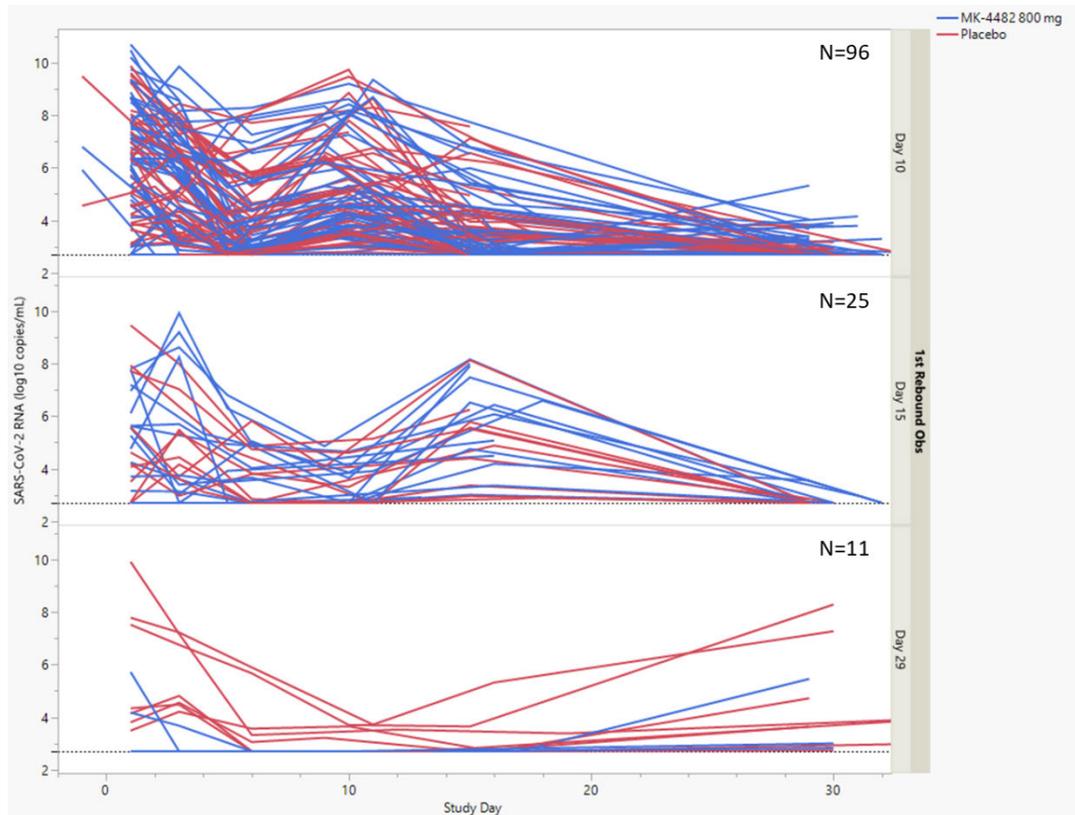


Figure 4. Viral RNA levels in NP samples for individual subjects according to timing of first analysis visit with observation of post-treatment SARS-CoV-2 RNA rebound (Day 10, 15 or 29).

Post-treatment viral RNA rebound was not associated with positive cell culture infectivity. The sponsor previously conducted and reported cell culture infectivity analyses from NP samples collected throughout the study. Most analyses were conducted on samples with viral RNA $>10^5$ copies/mL, and samples with viral RNA $<10^5$ copies/mL were imputed as undetected (<200 PFU/mL) based on the nearly universal lack of positive infectivity results in samples with viral RNA $<10^6$ copies/mL. Of the 129 subjects with post-treatment viral RNA rebound who had reported cell culture infectivity results (observed or imputed) for Day ≥ 10 NP samples, only 1 sample tested positive for cell culture infectious virus. This was from a Day 10 sample from MOV recipient subject 160300011, with a cell culture infectious virus titer of 15,840 PFU/mL and a relatively high viral RNA titer of 1.1×10^8 copies/mL. Another 75 Day ≥ 10 NP samples with RNA levels of 10^4 - 10^9 copies/mL were tested and all were negative for cell culture infectious virus.

There was no clear association between post-treatment viral RNA rebound and the primary clinical outcome of hospitalization or death through Day 29. Of the 132 subjects with post-treatment viral RNA rebound, 9 (7%) subjects, including 6 placebo recipients and 3 MOV recipients, reached the clinical endpoint of hospitalization or death through Day 29, 2 of whom died (1 MOV recipient, 1 placebo recipient). For comparison, the rate of hospitalization or death among subjects who did not experience virologic rebound was 6% (68/1118). There was no consistent pattern regarding the timing of hospitalization or death and post-treatment viral RNA rebound (Figure 5, FDA analysis).

**DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW**
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

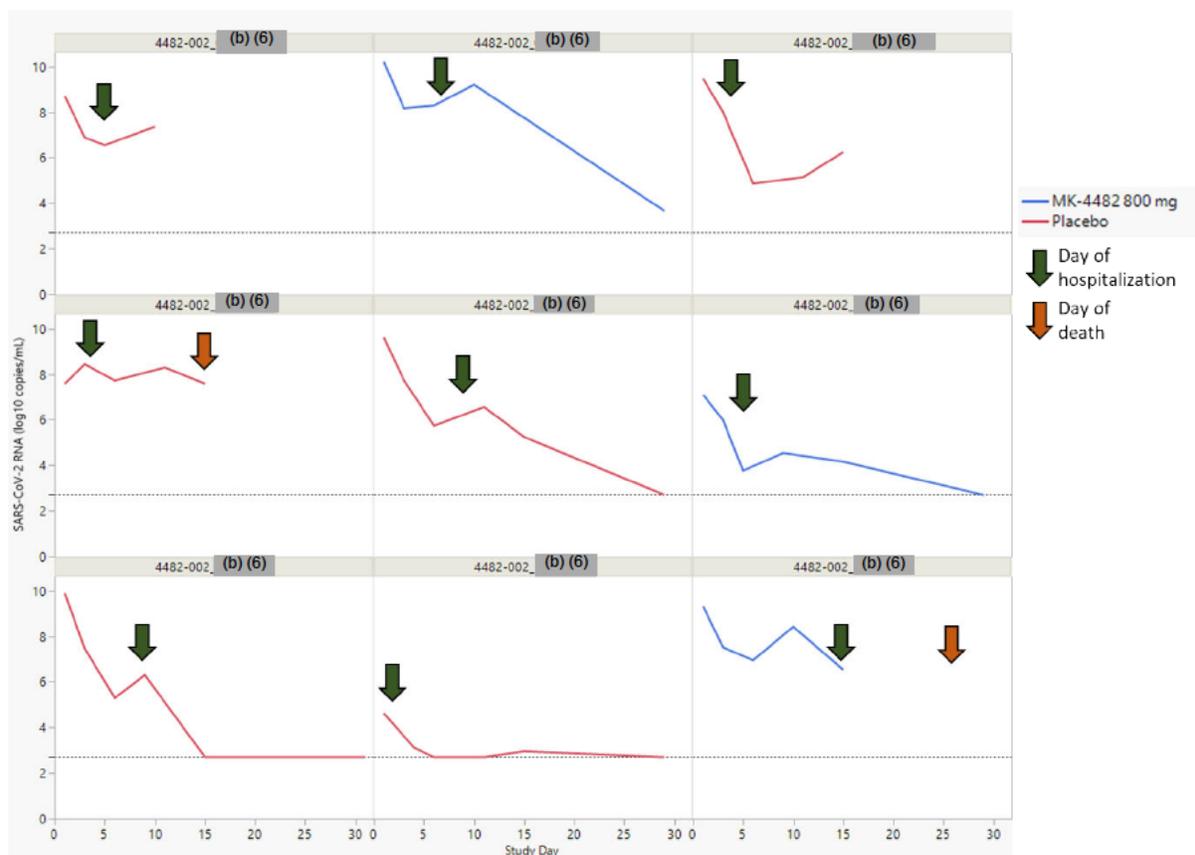


Figure 5. Viral RNA levels in NP samples for individual subjects with evidence of post-treatment SARS-CoV-2 RNA rebound who reached the primary clinical outcome of hospitalization or death through Day 29.

The rate of post-treatment (or post-Day 5 for placebo recipients) viral RNA rebound appeared to be numerically lower among subjects who were infected with a SARS-CoV-2 Delta variant, although there was no evidence that viral RNA rebound (or lack thereof) was specific to any SARS-CoV-2 variant(s) represented in the trial (Table 3; FDA analysis). Note that no subjects were infected with an Omicron variant.

Table 3. Proportion of subjects with post-treatment viral RNA rebound according to SARS-CoV-2 WHO variant. Analysis excludes subjects with other or unreported variants.

SARS-CoV-2 WHO Variant	MK-4482 800 mg	Placebo	All Subjects
Delta	9.0% (29/322)	7.5% (23/307)	8.3% (52/629)
Mu	19.7% (15/76)	15.9% (13/82)	17.7% (28/158)
Gamma	12.1% (4/33)	15.2% (7/46)	13.9% (11/79)
Alpha	23.5% (4/17)	0.0% (0/9)	15.4% (4/26)
Lambda	7.7% (1/13)	10.0% (1/10)	8.7% (2/23)
Beta	20.0% (1/5)	16.7% (1/6)	18.2% (2/11)

DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

Comment (internal): In the [SDN 121 Response Document](#) the sponsor confirmed the independent FDA analyses of viral RNA rebound described above were correct.

UPDATES TO APPROVED AVAILABLE ALTERNATIVES

On April 25, 2022, the indication for Veklury (remdesivir) was expanded to include pediatric patients (28 days of age and older and weighing at least 3 kg to less than 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Therefore, the Approved Available Alternatives section of the Lagevrio™ EUA Fact Sheet for Healthcare Providers is being updated to reflect the current approved indication. This revised indication for Veklury does not change the conclusion that Veklury is not considered an adequate alternative to Lagevrio since Veklury may not be feasible or practical for certain patients. It is important to note that Lagevrio is not authorized for use any pediatric patients.

CONCLUSIONS

Key conclusions from the sponsor's analyses and independent FDA analyses of post-treatment viral RNA rebound are as follows:

- Based on analyses conducted both by the sponsor and independently by FDA, rebounds in SARS-CoV-2 RNA levels in NP/nasal swab samples were observed in a subset of subjects following treatment with either molnupiravir or placebo in clinical trial MK-4482-002 (P002), Part 2.
- The sponsor identified subjects with symptomatic, post-treatment viral RNA rebound if they had viral RNA <LLOQ at Day 5 (EOT) or later, followed by a result that was >1 log₁₀ increase from this "negative" result (i.e., ≥5,000 copies/mL), AND had evidence of relapse and/or progression of at least 1 sign or symptom or hospitalization occurring within 1 visit relative to the visit in which the viral RNA rebound occurred. Based on these criteria, the sponsor identified a total of 14 participants (8/587 [1.4%] in the MOV group, and 6/566 [1.1%] in the placebo group) with symptomatic viral RNA rebound.
- The sponsor identified from the company's global safety database 8 molnupiravir treated subjects with possible disease recurrence, although limited details were available to investigate these cases.
- In FDA analyses of clinical trial MK-4482-002 (P002) Part 2 using a definition which maximizes sensitivity to detect post-treatment viral RNA rebound, irrespective of symptoms, post-treatment viral RNA rebound was observed in 10.8% (68/627) of molnupiravir recipients, and 10.3% (64/623) of placebo recipients (p=0.8, Fisher's Exact test).
- Post-treatment viral RNA rebound was not associated with positive cell culture infectivity. Of the 129 subjects with post-treatment viral RNA rebound who had reported cell culture infectivity results (observed or imputed) for Day ≥10 NP samples, only 1 sample tested positive for cell culture infectious virus.
- There was no clear association between post-treatment viral RNA rebound and the primary clinical outcome of hospitalization or death through Day 29. The rate of hospitalization or death

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CLINICAL VIROLOGY REVIEW
EUA#: [000108](#) SDNs: 112, 121, 126 REVIEW COMPLETED: 8/2/2022

among subjects with viral RNA rebound (7%) was similar to that of subjects who did not experience viral RNA rebound 6%. There was no consistent pattern regarding the timing of hospitalization or death and post-treatment viral RNA rebound.

- The rate of post-treatment (or post-Day 5 for placebo recipients) viral RNA rebound appeared to be numerically lower among subjects who were infected with a SARS-CoV-2 Delta variant, although there was no evidence that viral RNA rebound (or lack thereof) was specific to any SARS-CoV-2 variant(s) represented in the trial. Note that no subjects were infected with an Omicron variant.
- There are no clear, established molnupiravir resistance pathways in SARS-CoV-2, and therefore, no analyses were conducted assessing the relationship between post-treatment viral RNA rebound and molnupiravir resistance.
- Overall, these results indicate molnupiravir treatment did not contribute to a higher rate of post-Day 5 virologic rebound, and that the post-treatment viral RNA rebounds observed in molnupiravir recipients and placebo recipients likely reflect normal biological and/or technical variability in SARS-CoV-2 RNA levels in NP swab samples.

PROPOSED EDITS TO [LAGEVRIO™ FACT SHEET FOR HEALTHCARE PROVIDERS](#)

Based on the analyses and conclusions from this review, we proposed including new text in the LAGEVRIO EUA Fact Sheet for Healthcare Providers to summarize the post-treatment viral RNA rebound results from the MOVE-OUT trial (DAV [7/18/2022](#) communication). The sponsor accepted this language with no further changes ([SDN 121 Response Document](#) and proposed [revised HCP fact sheet](#)). The review team incorporated one minor editorial change for consistency, indicated below.

Viral RNA Rebound

Post-treatment increases in SARS-CoV-2 RNA shedding levels (i.e., viral RNA rebound) in nasopharyngeal samples were observed on Day 10, Day 15, and/or Day 29 in a subset of LAGEVRIO and placebo recipients in the Phase 3 MOVE-OUT trial. Approximately 1% of both SEE ATTACHED ADDENDUM and placebo recipients had evidence of recurrent COVID-19 symptoms coinciding with a rebound in viral RNA levels in nasopharyngeal samples.

Post-treatment viral RNA rebound was not associated with the primary clinical outcome of hospitalization or death through Day 29 following the single 5-day course of LAGEVRIO treatment. Post-treatment viral RNA rebound also was not associated with the detection of cell culture infectious virus in **NP-nasopharyngeal** swab samples.

In addition, the following changes are being implemented to reflect the current Veklury indication: APPROVED AVAILABLE ALTERNATIVES

Veklury (remdesivir) is FDA-approved for the treatment of COVID-19 in adults and pediatric patients **(at least 28 days old and weighing at least 3 kg ~~12-years-of-age-and-older-weighing-at-least-40-kg~~)** with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Veklury is administered via intravenous infusion for a total treatment duration of 3 days.

The sponsor accepted all of these fact sheet changes in [SDN 126 \(7/29/2022 revised HCP fact sheet\)](#).

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/s/

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08/04/2022 01:02:06 PM

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08/05/2022 06:00:43 AM

**EMERGENCY USE AUTHORIZATION REVIEW
US FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF INFECTIOUS DISEASES
DIVISION OF ANTIVIRALS
ADDENDUM**

EUA: 000108
Product: LAGEVRIO (molnupiravir)
Sponsor: Merck Sharp & Dohme LLC
Intended Population: Adults 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.

This addendum is for corrections to the summary EUA review for LAGEVRIO (molnupiravir) for the treatment of mild-to-moderate COVID-19 dated August 5, 2022.

The corrections are as follows:

On Page 1, the corrected Sponsor address should be:

“Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc. (Merck)
126 East Lincoln Ave
PO Box 2000
Rahway, NJ 07065”

On page 12, “LAGEGRIO” should be changed to “LAGEVRIO”

The corrections do not alter the conclusion of the review and do not alter the information presented in the authorized Facts Sheets for Healthcare Providers.

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/s/

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08/16/2022 11:22:03 AM

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