

Study Arm	Subject ID	Age Sex	Study Day of Death	Fatal AE Preferred Term(s)	Comments
PBO	(b) (6)	39 F	15	COVID-19 COVID-19 pneumonia	
PBO	(b) (6)	60 M	34	COVID-19 Septic Shock	Participant had pneumonia due to <i>Pseudomonas aeruginosa</i> requiring inotropic and vasopressor support.
PBO	(b) (6)	88 M	13	COVID-19 Respiratory failure	
PBO	(b) (6)	38 F	16	Acute respiratory failure	
PBO	(b) (6)	69 M	13	COVID-19 COVID-19 pneumonia	
PBO	(b) (6)	59 M	14	COVID-19 Respiratory failure	
PBO	(b) (6)	61 M	17	COVID-19	

Source: Narratives submitted in EUA request and in a Clinical Information Amendment dated December 3, 2021

^a The participants platelet count remained around baseline ($123 \times 10^9/L$) throughout his treatment with MOV. Then on Day 10 platelet count dropped to $80 \times 10^9/L$ and reached a nadir of $46 \times 10^9/L$ on Day 13. According to a hematology consultant, the thrombocytopenia was hemoperfusion-related. According to the Sponsor, the thrombocytopenia was also confounded by fluid shifts, sepsis, and numerous medications.

^b In the narrative submitted with the original EUA request this was reported as staphylococcal bacteremia and the SAE was subsequently recoded as staphylococcal sepsis. Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; F, female; ICU, intensive care unit; ID, identification; M, male; MOV, molnupiravir; PBO, placebo

3.3. Serious Adverse Events

SAEs were more common among placebo-treated participants (10%) compared to MOV-treated participants (7%). One placebo-treated participant and zero MOV-treated participants experienced an SAE that was assessed by the investigator to be drug-related (the drug-related SAE reported in the placebo-treated participant was pancreatitis). The SAEs reported in both arms are presented in [Table 17](#) below by system organ class (SOC) and preferred term (PT). COVID-19, COVID-19 pneumonia, or respiratory failure PTs accounted for the majority of SAEs in both arms, and all occurred at a greater frequency in the placebo arm than the MOV arm.

Table 17. Participants With Serious Adverse Events During Treatment and 14-Day Follow-Up Period, MK-4482-002, All Participants as Treated Population

System Organ Class Preferred Term	MOV N=710 n (%)	Placebo N=701 n (%)
Participants with one or more SAE	49 (6.9)	67 (9.6)
Blood and lymphatic system disorders	1 (0.1)	0
Thrombocytopenia	1 (0.1)	0
Cardiac disorders	0	2 (0.3)
Acute myocardial infarction	0	1 (0.1)
Atrial flutter	0	1 (0.1)
Gastrointestinal disorders	1 (0.1)	1 (0.1)
Pancreatitis	0	1 (0.1)
Pancreatitis acute	1 (0.1)	0
General disorders and administration site conditions	1 (0.1)	0
Edema peripheral	1 (0.1)	0
Infections and infestations	43 (6.1%)	61 (8.7)
Anal abscess	1 (0.1)	0
COVID-19	35 (4.9)	54 (7.6)
COVID-19 pneumonia	27 (3.8)	42 (6.0)
Lung abscess	1 (0.1)	0
Peritonitis	1 (0.1)	0
Pneumonia	2 (0.3)	0
Pneumonia aspiration	1 (0.1)	0
Pneumonia bacterial	3 (0.4)	2 (0.3)
Pneumonia haemophilus	0	1 (0.1)
Septic shock	0	1 (0.1)
Staphylococcal sepsis	0	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)	3 (0.4)
Diabetic ketoacidosis	1 (0.1)	1 (0.1)
Diabetic metabolic decompensation	0	1 (0.1)
Type 2 diabetes mellitus	0	1 (0.1)
Neoplasms benign, malignant, and unspecified	0	1 (0.1)
Metastases to lung	0	1 (0.1)
Nervous system disorders	1 (0.1)	0
Cerebral hemorrhage	1 (0.1)	0
Renal and urinary disorders	0	1 (0.1)
Acute kidney injury	0	1 (0.1)

System Organ Class	MOV	Placebo
Preferred Term	N=710	N=701
	n (%)	n (%)
Respiratory, thoracic, and mediastinal disorders	9 (1.3)	19 (2.7)
Acute respiratory failure	0	2 (0.3)
Cough	0	1 (0.1)
Dyspnea	0	1 (0.1)
Hiccups	0	1 (0.1)
Hypoxia	1 (0.1)	1 (0.1)
Pneumomediastinum	0	1 (0.1)
Pneumothorax	1 (0.1)	0
Pulmonary embolism	1 (0.1)	1 (0.1)
Pulmonary hypertension	0	1 (0.1)
Respiratory distress	0	1 (0.1)
Respiratory failure	6 (0.8)	9 (1.3)
Vascular disorders	1 (0.1)	0
Shock	1 (0.1)	0

Source: Clinical Information Amendment Dated December 3, 2021.

Abbreviations: COVID-19, coronavirus disease 2019; MOV, molnupiravir; SAE, serious adverse event

3.4. Dropouts and/or Discontinuations Due to Adverse Events

Treatment discontinuations due to AEs were more common among placebo-treated participants than MOV-treated participants. In total, there were 10 (1.4%) MOV-treated participants and 20 (2.9%) placebo-treated participants who experienced an AE leading to treatment discontinuation. The 10 AEs that lead to treatment discontinuation in MOV-treated participants were COVID-19 (n=3), nausea (n=2), vomiting (n=2), COVID-19 pneumonia, hypoxia, vision blurred, fatigue, peritonsillitis, tonsillitis, dizziness, headache, and urticaria (each reported in one participant unless otherwise noted). Of note, the tonsillitis and peritonsillitis AEs were reported in the same participant who had a reported history of chronic tonsillitis.

3.5. Common Adverse Events

AEs were reported in 216 (30.4%) and 231 (33.0%) of MOV- and placebo-treated participants, respectively. [Table 18](#) displays AEs reported by SOC and PT, in at least 1% of participants in either treatment arm. The Gastrointestinal disorders SOC and Infections and infestations SOC contained the largest proportion of AEs reported among MOV-treated participants. COVID-19 was the most common PT reported in both arms. The only PT slightly more common among MOV-treated participants than among placebo-treated participants was nausea. In addition, at the SOC level, there was a slightly larger proportion of MOV-treated participants reporting AEs in the Metabolism and nutrition disorder SOC, Nervous system SOC, and Skin and subcutaneous tissue disorders SOC than placebo-treated participants.

Table 18. Analysis of Participants With Adverse Events During Treatment and 14-Day Follow-Up Period (Incidence ≥1% of Participants in One or More Treatment Groups), MK-4482-002, All Participants as Treated Population

System Organ Class Preferred Term	MOV N=710 n (%)	Placebo N=701 n (%)
Participants with one or more AE	216 (30.4)	231 (33.0)
Gastrointestinal disorders	43 (6.1)	52 (7.4)
Diarrhea	16 (2.3)	21 (3.0)
Nausea	13 (1.8)	6 (0.9)
General disorders and administration site conditions	6 (0.8)	7 (1.0)
Infections and infestations	93 (13.1)	119 (17.0)
COVID-19	56 (7.9)	69 (9.8)
COVID-19 pneumonia	45 (6.3)	67 (9.6)
Pneumonia bacterial	14 (2.0)	11 (1.6)
Investigations	35 (4.9)	49 (7.0)
Alanine aminotransferase increased	12 (1.7)	12 (1.7)
Aspartate aminotransferase increased	2 (0.3)	8 (1.1)
Metabolism and nutrition disorders	16 (2.3)	12 (1.7)
Musculoskeletal and connective tissue disorders	7 (1.0)	11 (1.6)
Nervous system disorders	19 (2.7)	13 (1.9)
Dizziness	10 (1.4)	9 (1.3)
Psychiatric disorders	13 (1.8)	10 (1.4)
Respiratory, thoracic, and mediastinal disorders	12 (1.7)	28 (4.0)
Respiratory failure	6 (0.8)	9 (1.3)
Skin and subcutaneous tissue disorders	17 (2.4)	8 (1.1)
Vascular disorders	12 (1.7)	10 (1.4)
Hypertension	9 (1.3)	7 (1.0)

Source: Clinical Information Amendment Dated December 3, 2021

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 2019; MOV, molnupiravir

The majority of AEs were Grades 1 and 2 in severity. Grade 3 AEs were reported in 46 (6.5%) and 39 (5.6%) MOV- and placebo-treated participants, respectively. Grade 4 AEs were reported in 6 (0.8%) and 20 (2.9%) MOV- and placebo-treated participants, respectively. The majority of the Grades 3 and 4 AEs reported among MOV-treated participants were in the Infections SOC (specifically the PTs COVID-19 and COVID-19 pneumonia). The non-COVID-19 Grade 4 AEs reported among MOV-treated participants were lung abscess, pneumonia bacterial, diabetic ketoacidosis, pulmonary embolism, respiratory failure, and shock, each reported in one patient.

The majority of AEs were not assessed by the investigator to be drug-related. Only 8.0% and 8.4% of participants in the MOV and placebo arms, respectively, experienced a drug-related AE. Drug-related AEs occurring in at least 1% of participants in either arm are displayed in [Table 19](#) below. As shown, the rates of the most common drug-related AEs all occurred at a similar rate in the MOV and placebo arms.

Table 19. Drug-Related Adverse Events Occurring in ≥1% of Participants in One or More Treatment Groups During Treatment and 14-Day Follow-Up Period, MK-4482-002, All Participants as Treated Population

Preferred Term	MOV N=710 n (%)	Placebo N=701 n (%)
Participants with one or more drug-related AEs	57 (8.0)	59 (8.4)
Diarrhea	12 (1.7)	15 (2.1)
Nausea	10 (1.4)	5 (0.7)
Dizziness	7 (1.0)	5 (0.7)

Source: Efficacy Information Amendment dated December 3, 2021.

Abbreviations: AE, adverse event; MOV, molnupiravir

3.6. Adverse Events of Special Interest

As noted previously, fulfillment of Hy's Law criteria and any postbaseline platelet value <50,000/μL were prespecified ECIs. Two participants had an ECI reported in the all participants as treated population; one participant in the MOV group and one participant in the placebo group, both of whom had confirmed platelet counts of <50,000 cells/μL. This section provides an expanded discussion of hepatic and hematologic events and laboratory abnormalities as adverse events of special interest.

Hepatic Events

The only AEs under the hepatobiliary disorders SOC reported among MOV-treated participants were hypertransaminasemia and jaundice, which occurred in one MOV-treated participant each. The jaundice AE was assessed as drug-related. No hepatobiliary AEs were serious or led to treatment discontinuation. Grade 3 abnormalities in liver function test parameters were uncommon and occurred at a similar rate across arms (see [Table 20](#)). There was one Grade 4 ALT elevation reported among an MOV-treated participant, and no participants in either arm experienced a Grade 4 AST or bilirubin abnormality. No participants in either arm met Hy's Law criteria.

Hematologic Events

Severe decreases in bone marrow cellularity with associated decreases in all hematopoietic cell lines was observed in dog studies. Therefore, all hematologic AEs are of interest.

- Two MOV-treated participants experienced clinical neutropenia AEs (under the Blood and lymphatic system disorders SOC). One clinical neutropenia event was Grade 2 and the other was Grade 3 in severity. The Grade 2 event, but not the Grade 3 event, was assessed to be drug-related. Neither event led to treatment discontinuation. No clinical neutropenia AEs were reported in placebo-treated participants.
- The following bleeding AEs were reported: heavy menstrual bleeding and epistaxis, which both occurred in one placebo-treated participant each, and gingival bleeding, vessel puncture site hemorrhage, and cerebral hemorrhage each reported in one MOV-treated participant. None of these bleeding adverse events were temporally associated with thrombocytopenia or anemia, with the exception of the cerebral hemorrhage event which occurred in a participant with thrombocytopenia. See [Table 16](#) on fatal adverse events for additional details regarding this participant.

3.7. Laboratory Findings

As shown in [Table 20](#) below, Grades 3 and 4 chemistry laboratory abnormalities were uncommon overall and were generally balanced across treatment groups. Although not shown, Grades 1 and 2 chemistry laboratory abnormalities either occurred at a similar rate in both groups or occurred more frequently in the placebo group, with the exception of Grade 2 creatinine abnormalities which occurred in 7.9% of MOV-treated participants and 4.9% of placebo-treated participants.

Table 20. Grades 3 and 4 Abnormalities in Select Chemistry Laboratory Parameters, MK-4482-002, All Participants as Treated Population

Laboratory Parameter	MOV N=710 n/m (%)	Placebo N=701 n (%)
Alanine Aminotransferase (IU/L)		
Grade 3	7/609 (1.1)	10/621 (1.6)
Grade 4	1/609 (0.2)	0/621 (0)
Aspartate Aminotransferase (IU/L)		
Grade 3	5/659 (0.8)	3/651 (0.5)
Grade 4	0/659 (0)	0/651 (0.0)
Bilirubin (mg/dL)		
Grade 3	0/661 (0)	0/657 (0)
Grade 4	0/661 (0)	0/657 (0)
Creatine Kinase (IU/L)		
Grade 3	3/655 (0.5)	3/646 (0.5)
Grade 4	1/655 (0.2)	2/646 (0.3)
Creatinine (mg/dL)		
Grade 3	11/659 (1.7)	13/658 (2.0)
Grade 4	2/659 (0.3)	4/658 (0.6)
Lipase (IU/L)		
Grade 3	3/659 (0.5)	3/655 (0.5)
Grade 4	0/659 (0)	4/655 (0.6)

Source: Clinical Information Amendment dated December 3, 2021.

Abbreviations: m, number of participants with a baseline and at least one postbaseline test result; MOV, molnupiravir; n, number of participants with on-treatment postbaseline test results that met the predetermined criterion and are worse in grade than at baseline

Given the early safety signal for bone marrow toxicity in dogs, careful evaluation of abnormalities in hematologic parameters in patients is warranted. Therefore, [Table 21](#) includes all Grade hematology laboratory abnormalities. A slightly greater proportion of MOV-treated participants compared to placebo-treated participants experienced any grade hemoglobin abnormalities, though most of these were Grades 1 or 2 in severity and these abnormalities are not thought to be clinically meaningful. Grades 3 and 4 hematology laboratory abnormalities were rare and generally balanced across treatment groups (except for Grades 3 and 4 lymphocyte abnormalities which were more common in the placebo group and may have been confounded by COVID-19-associated lymphopenia). Please see Section [IX.3.6](#) for a detailed discussion of hematologic adverse events and laboratory abnormalities.

Table 21. Abnormalities in Select Hematology Laboratory Parameters, MK-4482-002, All Participants as Treated Population

Laboratory Parameter	MOV N=710 n/m (%)	Placebo N=701 n (%)
Hemoglobin (g/dL)		
Any Grade	25/615 (4.1)	16/616 (2.6)
Grade 1	13/615 (2.1)	10/616 (1.6)
Grade 2	10/615 (1.6)	2/616 (0.3)
Grade 3	2/615 (0.3)	4/616 (0.6)
Grade 4	0/615 (0)	0/616 (0)
Lymphocytes (10⁹/L)		
Any Grade	27/610 (4.4)	41/616 (6.7)
Grade 1	8/610 (1.3)	3/616 (0.5)
Grade 2	7/610 (1.1)	16/616 (2.6)
Grade 3	8/610 (1.3)	16/616 (2.6)
Grade 4	4/610 (0.7)	6/616 (1.0)
Neutrophils (10⁹/L)		
Any Grade	8/446 (1.8)	12/435 (2.8)
Grade 1	5/446 (1.1)	10/435 (2.3)
Grade 2	3/446 (0.7)	2/435 (0.5)
Grade 3	0/446 (0)	0/435 (0)
Grade 4	0/446 (0)	0/435 (0)
Platelets (10⁹/L)		
Any Grade	15/607 (2.5)	27/605 (4.5)
Grade 1	11/607 (1.8)	18/605 (3.0)
Grade 2	4/607 (0.7)	8/605 (1.3)
Grade 3	0/607 (0)	0/605 (0)
Grade 4	0/607 (0)	1/605 (0.2)
Leukocytes (10⁹/L)		
Any Grade	15/615 (2.4)	12/616 (1.9)
Grade 1	13/615 (2.1)	10/616 (1.6)
Grade 2	0/615 (0)	1/616 (0.2)
Grade 3	2/615 (0.3)	1/616 (0.2)
Grade 4	0/615 (0)	0/616 (0)

Source: Clinical Information Amendment dated December 3, 2021.

Abbreviations: m, number of participants with a baseline and at least one postbaseline test result; MOV, molnupiravir; n, number of participants with on-treatment postbaseline test results that met the predetermined criterion and are worse in grade than at baseline

3.8. Supporting Safety Data From Other Outpatient Trials

In Part 1 of MK-4482-002, 76 outpatients with mild-to-moderate COVID-19 were randomized to the MOV 800 mg arm and 74 participants were included in the MOV 800 mg safety population. There were no deaths in the MOV 800 mg arm and one (1.4%) death in the placebo arm. The proportion of participants experiencing an SAE was the same in the MOV 800 mg arm (4/74, 5.4%) and the placebo arm (4/74, 5.4%). The four SAEs reported among participants receiving MOV 800 mg were COVID-19 pneumonia (n=3) and pneumonia (n=1). None of the SAEs were assessed to be drug-related. Three (4.1%) participants in the MOV 800 mg arm and one (1.4%) participant in the placebo arm discontinued study drug due to an adverse event. The three discontinuations in the MOV 800 mg arm were due to the following four AEs: COVID-19 pneumonia (n=2), hypoesthesia, and insomnia. Lastly, no participants in the MOV 800 mg arm experienced any graded hemoglobin, lymphocyte, or platelet laboratory abnormalities.

In MK-4482-006, 55 outpatients with mild-to-moderate COVID-19 were randomized to receive MOV 800 mg, and all 55 participants were included in the safety analyses. There were no deaths reported in this trial. One (1.8%) MOV 800 mg–treated participant and one (1.6%) placebo-treated participant experienced an SAE (the SAE reported by the MOV-treated participant was acute respiratory failure that occurred on Day 2 of study drug and was not assessed to be treatment related but led to study-drug discontinuation). One (1.8%) MOV 800 mg–treated participant (see prior summary of the acute respiratory failure SAE) and one (1.6%) placebo-treated participant discontinued study drug due to an AE. Grades 1 and 2 hemoglobin laboratory abnormalities were more common among MOV 800 mg–treated participants (5.7%) than placebo-treated participants (1.6%). No graded lymphocyte or platelet abnormalities were reported among MOV 800 mg–treated participants. No Grades 3 or 4 abnormalities in any hematologic laboratory parameters were reported across the trial.

No new safety signals were identified in these supportive data from outpatient trials of adults with mild-to-moderate COVID-19.

3.9. Experience in Hospitalized Patients

MK-4482-001, was a Phase 2/3 trial of MOV in hospitalized adults with COVID-19. The overall trial design was very similar to that of MK-4482-002. Upon completion of interim analysis 2 (conducted when all of the participants in the Part 1/Phase 2 portion of the trial had reached study Day 29), the Sponsor decided not to initiate Part 2/Phase 3 of the trial because data indicated that “MOV is unlikely to demonstrate a clinical benefit in hospitalized participants, who generally have a long duration of symptoms prior to study entry.”

In Part 1 of the trial 72 participants received MOV 800 mg orally Q12H for 5 days and will therefore contribute to the safety database for this EUA request. However, in addition, as there is an imbalance in fatal AEs in this study when all MOV dose cohorts are analyzed, some analyses will be presented including participants who received lower doses of MOV to allow for a comprehensive assessment of this imbalance.

As shown in [Table 22](#), when combining all MOV dose cohorts, the rates of AEs and SAEs were higher among placebo-treated participants than among MOV-treated participants. However, the overall rate of fatal AEs was higher among MOV-treated participants (6.4%) than among placebo-treated participants (2.7%). If just the MOV 800 mg group is considered, the rates of AEs, SAEs, and fatal AEs were all higher among MOV-treated participants than placebo-treated participants. Interestingly, the rate of fatal AEs was highest in the MOV 200 mg group, where the rate was approximately 3 times higher than the rate of fatal AEs observed in the placebo arm. Notably, there were no imbalances in baseline characteristics to account for the high rate of deaths in the MOV 200 mg group. However, the proportion of participants with severe COVID-19 at baseline (as opposed to mild-to-moderate) was highest in the MOV 800 mg arm (53.9% and 42.3% in the MOV 800 mg and placebo arms, respectively) and could account for some of the imbalance in deaths between the MOV 800 mg group and the placebo group.

Table 22. Adverse Event Summary During Treatment and 14-Day Follow-Up Period, MK-4482-001, IA2, All Participants as Treated Population

Adverse Event Category	MOV 200 mg (N=73)	MOV 400 mg (N=73)	MOV 800 mg (N=72)	MOV All (N=218)	Placebo (N=75)
Any AE	40 (54.8)	36 (49.3)	45 (62.5)	121 (55.5)	46 (61.3)
AEs related ^a to study drug	8 (11.0)	6 (8.2)	10 (13.9)	24 (11.0)	16 (21.3)
AEs leading to discontinuation of study drug	0	1 (1.4)	0	1 (0.5)	0
Any SAE	11 (15.1)	9 (12.3)	13 (18.1)	33 (15.1)	12 (16.0)
SAEs related ^a to study drug	1 (1.4)	0	0	1 (0.5)	0
SAEs leading to discontinuation of study drug	0	1 (1.4)	0	1 (0.5)	0
Fatal SAEs	6 (8.2)	4 (5.5)	4 (5.6)	14 (6.4)	2 (2.7)

Source: P001v01 CSR submitted to IND 147734, Table 12.1

^a Determined by the investigator to be related to the drug

Abbreviations: AE, adverse event; IA2, interim analysis 2; MOV, molnupiravir; SAE, serious adverse event

Deaths

As previously noted, the rate of fatal AEs was higher in the overall MOV group and the MOV 800 mg group compared to the placebo group. Across all MOV dose groups, there was a total of 14 fatal AEs, none of which were assessed to be study drug–related. [Table 23](#) below summarizes the fatal AEs. As shown, the deaths largely occurred in older participants with multiple comorbidities. Many deaths occurred long after study drug had been completed. Based on review of the narratives, the clinical reviewer agrees with the assessment that none of the events were likely study drug–related. All fatal AEs appear to have been either directly or indirectly related to COVID-19.

Numerous secondary infections were reported. Complete hematologic laboratory data were not available for all patients. However, based on available data, leukocytosis and lymphopenia were common among participants who experienced a fatal AE in both arms. The universal steroid use among these participants likely contributed to the observed leukocytosis and may have increased their risk of infection. Among the participants with lymphopenia, the low lymphocyte count was typically present at screening, suggesting that the abnormality was more likely attributable to SARS-CoV-2 (which is known to be associated with lymphopenia) than to MOV.

Table 23. Summary of Fatal Adverse Events, MK-4482-001, IA2

Study Arm	Subject ID	Age and Sex	High Risk Criteria	Concomitant COVID-19 Treatment	Preferred Term	Study Day of AE Onset Relative to Treatment	Study Day of Death	Comments
MOV 200 mg	(b) (6)	61 F	Age >60, Coronary artery disease, diabetes, and obesity	Steroids	Respiratory failure	5	22	Intubated on Day 6. Also had acute kidney injury and bacteremia SAEs.
MOV 200 mg	(b) (6)	55 F	Diabetes	Steroids	Bacteremia	15	17	Intubated on Day 12. Also had hemorrhoids, hemoglobin decreased, and peritonitis bacterial SAEs. Blood and peritoneal fluid cultures grew <i>Streptococcus pneumoniae</i> . Leukopenia noted on Day 3, resolved by Day 9.
MOV 200 mg	(b) (6)	72 M	Age >60, obesity	Steroids	COVID-19	10	31	Intubated on Day 10. Also had a pneumothorax SAE. Course complicated by <i>Klebsiella pneumoniae</i> bacteremia and multiorgan dysfunction.
MOV 200 mg	(b) (6)	67 F	Age >60, chronic kidney disease, obesity, and diabetes	Steroids	Respiratory failure, COVID-19	2	17	On Day 8 high-flow oxygen was started. On Day 15 a DNR order was written, and patient was transferred to palliative care.
MOV 200 mg	(b) (6)	71 M	Age >60, obesity, diabetes, coronary artery disease	Steroids, remdesivir	Acute respiratory failure, COVID-19	11 15	16	Noninvasive mechanical ventilation was started on Day 2. On Day 11, ECMO was started.
MOV 200 mg	(b) (6)	73 F	Age >60, chronic kidney disease, DM	Steroids, remdesivir	Pneumonia bacterial, COVID-19	13	37	Intubated on Day 17. She was treated for bacterial pneumonia with no improvement. On Day 37 decision was made "not to prolong treatment", she was transferred to the general ward and died that day.

Study Arm	Subject ID	Age and Sex	High Risk Criteria	Concomitant COVID-19 Treatment	Preferred Term	Study Day of AE Onset Relative to Treatment	Study Day of Death	Comments
MOV 400 mg	(b) (6)	69 F	Age >60, Obesity	Steroids	Shock	9	9	Intubated on Day 4. Blood cultures positive for <i>Staphylococcus aureus</i> and <i>Acinetobacter baumannii</i> .
MOV 400 mg		85 M	Age >60	Steroids	Septic Shock	15	18	Intubated on Day 13. Bacteremia and bacterial pneumonia were reported.
MOV 400 mg		69 M	Age >60	Steroids	COVID-19 pneumonia	5	8	Intubated on Day 8.
MOV 400 mg		71 M	Age >60, obesity, diabetes	Steroids, remdesivir	Cardiac arrest	8	8	Intubated on Day 7. On Day 8 was started on vasopressors and ultimately went into cardiac arrest. Respiratory failure, pneumonia, respiratory acidosis, lactic acidosis, and metabolic acidosis SAEs also reported.
MOV 800 mg		63 M	Age >60	Steroids	COVID-19 pneumonia	10	14	Started noninvasive mechanical ventilation on Day 3 and intubated on Day 12.
MOV 800 mg		52 M	None	Steroids	Acute Respiratory Distress Syndrome	1	16	Intubated on Day 1. Also had septic shock, hyponatremia, acute kidney injury, and cholestasis SAEs. <i>Klebsiella pneumoniae</i> and <i>Burkholderia cepacia</i> isolated from sputum.
MOV 800 mg		55 M	None	Steroids, Remdesivir	Acute respiratory Failure, COVID-19	2	38	Started noninvasive mechanical ventilation on Day 5 and was intubated on Day 14. Course complicated by DVT, acute kidney injury and pneumomediastinum. Family ultimately withdrew care.

Study Arm	Subject ID	Age and Sex	High Risk Criteria	Concomitant COVID-19 Treatment	Preferred Term	Study Day of AE Onset Relative to Treatment	Study Day of Death	Comments
MOV 800 mg	(b) (6)	65 M	Age >60, obesity	Steroids	Acute respiratory failure, COVID-19	3	19	Transferred to the ICU on Day 6 and intubated on Day 11. Patient also developed sepsis, multiorgan failure, thrombocytopenia, and gangrene of both feet. Angiogram of the legs showed bilateral obstruction of the femoral arteries and complete bilateral obstruction of the popliteal arteries. On Day 19 he underwent an urgent thrombectomy, later that day he became unstable and died.
Placebo	(b) (6)	86 M	Age >60	Steroids	Pulmonary sepsis	11	15	Intubated on Day 11. Experienced thrombocytopenia (nadir =32 x 10 ⁹).
Placebo	(b) (6)	70 F	Age >60, diabetes	Steroids, remdesivir, tocilizumab	COVID-19 pneumonia	3	31	Intubated on Day 3. Experienced a nonserious pulmonary embolism on Day 11 and ventilator associated pneumonia on Day 20.

Source: EUA request (narratives in file 06d99p.pdf)

Abbreviations: AE, adverse event; COVID-19, coronavirus disease 19; ECMO, extracorporeal membrane oxygenation; DVT, deep vein thrombosis; IA2, interim analysis 2; ICU, intensive care unit; MOV, molnupiravir; SAE, serious adverse event

Serious Adverse Events

Serious adverse events were reported in 15% of MOV-treated participants (overall) and 16% of placebo-treated participants. One participant in the MOV 200 mg intervention group had an SAE considered to be related to study intervention (Grade 3 urticaria). Among the participants who received MOV 800 mg, 13 (18.1%) experienced an SAE. SAEs reported in one or more participants in the MOV 800 mg cohort are listed in [Table 24](#) below in order of decreasing frequency. Though not shown, at the SOC level, SAEs in the Infections and infestations SOC were more common in the MOV 800 mg arm (15.3%) than the placebo arm (12.0%). The majority of these SAEs were COVID-19 and COVID-19 pneumonia PTs. SAEs in the Respiratory, thoracic, and mediastinal disorders SOC were more common in the placebo arm (9.3%) than the MOV 800 mg arm (8.3%).

Table 24. Serious Adverse Events Reported in One or More MOV-Treated Participants, MK-4482-001, IA2, All Participants as Treated Population

Preferred Term	MOV 800 mg N=72 n (%)	Placebo N=75 n (%)
Participants with one or more SAE	13 (18.1)	12 (16.0)
COVID-19	5 (6.9)	6 (8.0)
COVID-19 pneumonia	3 (4.2)	4 (5.3)
Respiratory failure	3 (4.2)	3 (4.0)
Pneumonia	2 (2.8)	0
Pneumonia bacterial	2 (2.8)	0
Acute respiratory failure	2 (2.8)	2 (2.7)
Physical deconditioning	1 (1.4)	0
Cholestasis	1 (1.4)	0
Septic shock	1 (1.4)	0
Urinary tract infection enterococcal	1 (1.4)	0
Transaminases increased	1 (1.4)	0
Hyponatremia	1 (1.4)	0
Acute kidney injury	1 (1.4)	0
Chronic kidney disease	1 (1.4)	0
Acute respiratory distress syndrome	1 (1.4)	0
Deep vein thrombosis	1 (1.4)	0

Source: MK-4482-001 CSR, Table 14.3-9

Abbreviations: COVID-19, coronavirus disease 19; IA2, interim analysis 2; MOV, molnupiravir; SAE, serious adverse event

Other Adverse Events

The only treatment-related AE (i.e., adverse drug reaction) reported in more than one MOV 800 mg participant was nausea (n=2, 2.8%).

No participants in the MOV 800 mg arm discontinued study drug due to an AE (one MOV 400 mg participant discontinued study drug due to an AE of respiratory failure).

As in MK-4482-002, prespecified events of clinical interest for MK-4482-001 were platelet count <50,000 μ L and fulfillment of Hy's Law criteria. One placebo-treated participant experienced a treatment-emergent platelet count <50,000 μ L and one MOV 800 mg participant met Hy's Law laboratory criteria. The participant with potential drug-induced liver injury only satisfied the criteria for 1 day and the following day the alkaline phosphatase increased, and the criteria were no longer met. The liver function test abnormalities were thought to be due to septic shock and cholestasis, not drug-induced liver injury.

Laboratory Findings

There were no concerning findings or apparent trends observed among chemistry laboratory parameters. The only Grade 4 chemistry abnormalities reported among participants receiving MOV 800 mg were glucose increased (n=4, more common among placebo patients) and potassium increased (n=1). Hematology laboratory abnormalities are shown in [Table 25](#) below. Hemoglobin abnormalities were overall more common among the MOV 800 mg arm than the placebo arm. Grade 2 and greater lymphocyte abnormalities were balanced across arms and Grade 2 and greater platelet abnormalities were slightly more common in the MOV arm than the placebo arm.

Table 25. Grades 3 and 4 Abnormalities in Select Hematology Laboratory Parameters, MK-4482-001, IA2, All Participants as Treated Population

Laboratory Parameter	MOV 800 mg N=72 n/m (%)	Placebo N=75 n (%)
Hemoglobin decreased (g/dL)		
Any Grade	11/49 (22.4%)	4/48 (8.3)
Grade 1	4/49 (8.2)	1/48 (2.1)
Grade 2	4/49 (8.2)	2/48 (4.2)
Grade 3	3/49 (6.1)	1/48 (2.1)
Grade 4	0	0
Lymphocytes decreased (10⁹/L)		
Any Grade	5/49 (10.2)	4/48 (8.3)
Grade 1	0	0
Grade 2	2/49 (4.1)	1/48 (2.1)
Grade 3	0	2/48 (4.2)
Grade 4	3/49 (6.1)	1/48 (2.1)
Absolute neutrophil count decreased (10⁹/L)		
Any Grade	0	0
Grade 1	0	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0
Platelets decreased (10⁹/L)		
Any Grade	4/49 (8.2)	1/45 (2.2)
Grade 1	1/49 (2.0)	0
Grade 2	3/49 (6.1)	0
Grade 3	0	1/45 (2.2)
Grade 4	0	0
Leukocytes decreased (10⁹/L)		
Any Grade	0	0
Grade 1	0	0
Grade 2	0	0
Grade 3	0	0
Grade 4	0	0

Source: MK-4482-001 CSR, Table 14.3-15 and response to IR submitted October 26, 2021.

For graded criteria: participants are counted once per test in the highest grade reported.

For inclusion in this analysis, both a baseline and at least one postbaseline laboratory value had to be present. Only participants with a worsened grade from baseline were included.

For the criteria that involve a comparison to baseline, a baseline value is also required.

Abbreviations: IA2, interim analysis 2; m, number of participants with at least one postbaseline test result; MOV, molnupiravir; N, number of participants in population; n number of participants with postbaseline test results that met the predetermined criterion and is worse in grade than at baseline

4. Key Review Issues Relevant to Evaluation of Risk

This section will describe the identified pharmacology/toxicology and virology review issues with respect to mutagenicity, bone growth and cartilage findings, embryo-fetal toxicity, effect of MOV on SARS-CoV-2 spike protein sequences, and potential MOV resistance or remdesivir cross-resistance in clinical trials.

4.1. Key Review Issue #1: Mutagenicity

Background

MK-4482 (MOV; EIDD-2801) and its metabolite (N4-hydroxycytidine; NHC; EIDD-1931) were positive for mutagenicity in in vitro Ames assays, but MOV was negative in a follow-up in vivo assay. Based on the weight of evidence and expert input, as well as the short-term use (5 days), the risk of mutagenicity following treatment with MOV is low.

Assessment

Mechanistically, the nucleoside triphosphate anabolite of MOV, NHC-TP, acts as a competitive, alternative substrate for the virally encoded RNA-dependent RNA polymerase. The apparent incorporation into nascent chain viral RNA results in increased mutational frequency in the viral genome, resulting in induction of viral error catastrophe and the production of nonviable virus. Given the mechanism of action, NHC-diphosphate could theoretically be transformed by ribonucleotide reductase in human cells to the 2'-deoxyribonucleotide form and the deoxynucleotide subsequently incorporated into cellular deoxyribonucleic acid (DNA), leading to DNA mutations. To assess the genotoxic (i.e., mutagenic) potential of MOV, a battery of in vitro and in vivo mutagenicity assays was conducted by the Sponsor according to International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. In addition, a 6-month carcinogenicity study in transgenic mice is ongoing.

Ames tests were conducted with the ester prodrug (MOV; EIDD-2801) and initial metabolite, NHC (EIDD-1931). EIDD-2801 was positive for mutagenicity in *Escherichia coli* strain WP2 uvrA and *Salmonella typhimurium* strain TA102, but negative in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. EIDD-1931 was positive for mutagenicity in *E. coli* strain WP2 uvrA, but negative in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537. EIDD-1931 was not tested with strain TA102. The in vivo and in vitro micronucleus assays showed negative results.

In a published report, NHC has been reported to cause gene mutations in a cultured animal cell line after an extended duration of exposure (32 days), which may occur through interactions with host ribonucleotide reductase and DNA polymerases (Zhou et al. 2021).

MOV was further evaluated in two established in vivo assays for mutagenicity: The Pig-a assay and the transgenic Big Blue[®] rat assay. Both assays are intended for hazard identification and are powered to detect a minimum increase in mutant frequency, approximately 50 to 100% above the negative control frequency. The Pig-a assay is capable of detecting missense mutations: Of the mutations identified that produce the Pig-a phenotype, the majority are missense mutations (R. Hoeflich, personal communication, December 11, 2021); however, any attempt to extrapolate from the frequencies of phenotypically glycosylphosphatidylinositol-

deficient (Pig-a mutant) erythrocytes that are measured by the assay to a quantitative assessment of mutation frequencies in the entire genome would be tenuous, at best.

The results of the Pig-a assay in reticulocytes and red blood cells, reflecting mutations induced in nucleated hematopoietic progenitor and stem cells, were “equivocal” (not clearly positive or negative) as the assay met only one of three acceptance criteria set in the draft test guidelines for the mammalian erythrocyte Pig-a gene mutation assay (OECD 2021). Specifically, a test chemical is considered clearly positive if all of the following criteria are met: (1) at least one of the treatment groups exhibits a statistically significant increase in the mutant reticulocyte (MUT RET) and mutant red blood cell (MUT RBC) frequency compared with the concurrent negative control; (2) the mutant frequency responses are dose-related when evaluated with an appropriate trend test; and (3) the MUT RET and/or MUT RBC frequency of any of the test chemical dose groups exceeds the upper bound limit of the historical negative control data distribution.

The results of the MOV Pig-a assay demonstrated significant increases in MUT RETs and MUT RBCs for dosed groups, which is consistent with a positive response. However, an apparent increasing response trend with dose was not statistically-significant, and the MUT RET and MUT RBC frequencies measured in MOV-treated groups did not exceed the upper bound limit of the historical negative control data distribution. Therefore, based on the draft Organisation for Economic Co-operation and Development criteria for evaluating Pig-a assay study data, the outcome of the assay was equivocal.

The Sponsor decided not to perform further analysis of the Pig-a endpoint to resolve this equivocal response, but rather to study the *in vivo* mutagenicity of MOV further by conducting another *in vivo* mutation assay, the transgenic rodent gene mutation assay using Big Blue[®] rats. In the transgenic Big Blue[®] rat model, the drug was evaluated for increased mutant frequency at the lambda cII transgene in liver and bone marrow. In that assay, MOV was clearly negative for mutagenicity.

Studies have demonstrated that nucleoside analog drugs are able to penetrate the blood-testes barrier (Reineke et al. 2001; Hu et al. 2021) and, therefore, exposure of male germ cells to NHC following treatment with MOV is possible. If NHC is detected in testes in an ongoing pharmacokinetic/distribution study in rats, an assessment of mutant frequencies in testicular germ cells from transgenic Big Blue[®] rats will be completed.

To confirm the relevance of exposure concentrations of the active metabolite (NHC-TP) used in the mutagenicity assays, the Agency requested tissue distribution data. The Sponsor submitted further data on NHC-TP concentrations in rat tissues and human peripheral blood mononuclear cells (PBMCs), as well as *in vitro* assays assessing species differences in the conversion of NHC to NHC-TP in PBMCs. Based on assessment of that information, Agency reviewers have concluded that rats were likely exposed to clinically relevant concentrations of NHC-TP during the *in vivo* mutagenicity assays.

A consult with colleagues from the Agency’s Center for Drug Evaluation and Research Pharmacology/Toxicology Genotoxicity Subcommittee (GSc) was submitted regarding the overall weight of evidence of the genotoxicity data. The GSc confirmed the Division’s conclusions that MOV and NHC were positive for mutagenicity in the *in vitro* bacterial reverse mutation (Ames) assay. The GSc also reaffirmed that the transgenic rodent (Big Blue[®] rat) study, and not the Pig-a study, was the primary assay for follow-up assessment of the Ames-positive findings. Lastly, the GSc confirmed that the negative response in the transgenic Big Blue[®] rat assay indicated that neither parent prodrug nor the metabolite NHC are *in vivo* mutagens. Therefore, the level of concern for mutagenicity in the clinical setting is low.

The GSc opined that the positive results in the Ames assay were likely due to incorporation of the NHC-TP ribonucleotide into bacterial DNA. If incorporation occurs in humans, DNA replicase/repair in eukaryotic cells is highly efficient (as contrasted to bacterial replicase/repair). The negative result from the in vivo transgenic Big Blue[®] rat assay confirms that the ribonucleoside analog is not an in vivo mutagen under the conditions of the assay.

As noted above, given the mechanism of action, it is theoretically possible that the 2'-deoxyribonucleotide form of NHC could be incorporated into cellular DNA, leading to DNA mutations. The available mutagenicity data from somatic cell assays indicate that MOV is not mutagenic in vivo, although a positive, but not statistically significant, trend and significant increases relative to the concurrent (but not historical) negative control were noted in the equivocal Pig-a assay. Limitations of the available nonclinical mutagenicity assays preclude a determination of no risk of mutagenicity, and the ongoing carcinogenicity study and planned testicular germ cell mutation assay (if NHC is detected in testes) will assess the risk to male patients beyond 90 days.

Based on the weight of evidence and expert input, as well as the short-term use (5 days), the risk of mutagenicity following treatment with MOV is considered low.

Conclusions

Pharmacology/Toxicology Team Perspective

The mutagenicity topic was raised repeatedly during the November 30, 2021, Advisory Committee meeting, and uncertainty about genotoxicity was cited as a cause for concern by Committee members who voted either “Yes” or “No” to the single voting question. A particular concern raised was the potential effect on male germ cells that could result in birth defects. As the in vivo mutagenicity assays performed to date use somatic cells (fully differentiated precursor, and stem cells from liver and bone marrow, and peripheral reticulocytes and red blood cells as reporter cells for mutation in nucleated hematopoietic progenitor and stem cells) and not germ cells (eggs and sperm), the ability for MOV to induce mutations in germ cells has not been directly assessed. Somatic cell assays may represent a worst-case, as male germ cells, while reproductively active in adults, appear to be relatively protected from mutagenic DNA damage, including having more efficient DNA repair mechanisms than do somatic cells (Olsen et al. 2001). However, the capacity for DNA repair appears to wane as spermatogonia mature to sperm (Marchetti and Wyrobek 2008) in a process that takes 74 days in humans.

Repair mechanisms such as mismatch repair and homologous recombination that are active in the earliest phases of spermatogenesis give way to the more error-prone nonhomologous end joining process in spermatids (Garcia-Rodriguez et al. 2018). Thus, additional studies to discern the potential effects of MOV on male germ cells may be warranted: If NHC is detected in testes in an ongoing pharmacokinetic/distribution study in rats, a nonclinical assessment of mutant frequencies in testicular germ cells will be completed in early 2023. Results from a carcinogenicity study are expected by the end of 2022. Male germ cell (sperm) maturation starts in early puberty and the sperm maturation process takes 74 days; a period covered by the use of contraception for 90 days in males of reproductive potential who are exposed to MOV. The carcinogenicity study and the testicular germ cell mutation assay will provide data regarding the risk to male patients, and their offspring, beyond 90 days. SEE ATTACHED ADDENDUM

The risk of MOV use in individuals of childbearing potential is mitigated by the recommendation for the use of contraception during MOV treatment and for 4 days after the end of treatment.

For information regarding MOV use during pregnancy, please see Section 4.3 for a discussion of the complex benefit:risk considerations.

The consensus of the Pharmacology/Toxicology review team, based on the weight of evidence and expert opinion, is that the potential for MOV to cause mutagenicity in humans is low, and the risk of mutagenicity is further reduced by the short 5-day treatment duration. The risk of MOV use in individuals of reproductive potential is mitigated by the use of contraception for 9 days in exposed females, and the use of contraception for 90 days in exposed males. MOV is recommended to be authorized for use in high risk COVID-19 infected adults for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Until additional data are provided to inform the risk to male germ cells, the Fact Sheet for Health Care Providers should state, “While the risk is regarded as low, studies to fully assess the potential for MOV to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of MOV. The risk beyond 3 months after the last dose of MOV is unknown.”

Also, the Division recommends that the treatment duration be limited to 5 days (10 doses). To this end, MOV will be dispensed in a container containing enough tablets for exactly one treatment course. Additionally, MOV is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

Clinical Virology Team Leader Perspective

This reviewer is concerned about the impact on the human germline of MOV mutations in regenerating spermatogonial stem cells and meiotic cells (multiple replication cycles in the 16 days to meiosis I) during spermatogenesis. Human males produce approximately 100 million sperm/day (Amann and Howards 1980) with each sperm produced having more than a billion base pairs at which a mutagen could act (Chial et al. 2008).

NHC diphosphate is an obligate intermediate in the formation of the active metabolite of MOV and may be converted by ribonucleotide reductase to dNHC diphosphate which subsequently is incorporated into DNA after phosphorylation to the triphosphate. Incorporation of dNHC phosphate into DNA would lead to mutations in the same way that NHC leads to mutations in RNA. At some level this appears to occur as MOV has shown the potential to be a DNA mutagen to eukaryotic cells in one independent study (Zhou et al. 2021).

The Sponsor conducted studies in rodents to assess MOV’s mutagenicity using the Pig-a and Big Blue® assays. The Pig-a assay is considered the more sensitive assay for evaluating mutagens as the signal to noise ratio is higher. Spermatogenesis cannot be directly evaluated in this assay but generation of reticulocytes, which lack a nucleus, can be considered a surrogate as their phenotype represents mutations in regenerating stem cells and replicating intermediate cells. Looking at the reticulocyte results in the Pig-a assay, MOV showed a dose/response ranging from 5.52 pig-a mutations/million cells for the lowest dose to 10.98 pig-a mutations/million cells for the highest dose with a concurrent control value of 4.97 pig-a mutations/million cells.

Results from the Sponsor’s Pig-a assay were considered equivocal with two possible interpretations of the results from the Pig-a assay as presented. In the first case, the result is a low level positive and compared to positive controls, MOV is a weak mutagen. Alternatively, MOV is negative in this assay. Both results are concerning. For the first interpretation where

MOV is a weak mutagen, these results indicate that MOV could increase the number of germline mutations. The alternative interpretation that the difference between 4.97/million cells and 10.98/million cells isn't significant raises the question as to whether the assay is sensitive enough to detect a rate of mutagenesis (e.g., ~2-fold) that would be concerning with respect to the germline.

When queried, FDA personnel working with these assays were unable to provide the limit of detection of the assay with respect to the relative increase in the number of mutations/genomes replicated. It should be noted that the Pig-a assay is designed to identify only null mutations, and NHC predominantly causes transition mutations which frequently may not result in the incorporation of stop codons or major functional changes that might lead to a null phenotype in the assay, so the actual rate of mutations may be higher than observed.

As noted above, the rate of germline mutations introduced by MOV is unknown. Furthermore, it is unclear what rate would be acceptable in the context of thirty-four individuals being exposed for each individual who benefits (i.e., number needed to treat to prevent one hospitalization or death). Given the ongoing pandemic and emerging variants, this reviewer agrees with the recommendation of the review team of authorization as there may be situations when alternative therapies are not accessible or clinically appropriate. In such cases, male patients should be counseled that there may be risks beyond 3 months due to mutations in spermatogonial stem cells so they can make an informed decision.

Review Memo, Senior Signatory Perspective

I concur with the assessment of the pharmacology toxicology review team that the potential for MOV to cause mutagenicity in humans is low, and the risk of mutagenicity is further reduced by the short 5-day treatment duration. I agree with the assessment of the clinical virology team leader and the pharmacology toxicology review team that additional data are needed to inform the risk to male germ cells, and note that the Sponsor will prioritize completion of a carcinogenicity study and a testicular germ cell mutation assay. Until these data are available, we have an obligation to be as transparent as possible with health care providers and patients.

I recommend that the Fact Sheet for Patients and Caregivers include the following information:

- For individuals who are sexually active with partners who are able to become pregnant:
 - It is not known if MOV can affect sperm, which may cause harm to your unborn baby. While the risk is regarded as low, studies to fully assess the potential for MOV to affect offspring of treated males have not been completed. You should use a reliable method of birth control (contraception) consistently and correctly during treatment with MOV and for at least 3 months after the last dose. The risk to sperm beyond 3 months is not known. Talk to your health care provider about reliable birth control methods. Talk to your health care provider if you have questions or concerns about how MOV may affect sperm cells.

I conclude that the above recommendations for the Fact Sheet for Patients and Caregivers appropriately convey the uncertainty and risk.

4.2. Key Review Issue #2: Bone/Cartilage Formation-Related Findings

Background

MOV may affect bone and cartilage development. In a chronic (3-month) rat study, abnormal bone (growth plate) and cartilage formation were noted. Also, in embryo-fetal development (EFD) studies in rats and rabbits, delayed and incomplete ossification was noted in fetuses. Systemic exposures in pregnant rats and rabbits were approximately 8- and 7-fold, respectively, the mean clinical NHC exposure at 800 mg Q12H. As a result of the concerns related to bone and cartilage formation in development, the Sponsor is conducting a study to assess developmental effects of MOV in juvenile rats.

Assessment

Physis and Epiphysis Findings in Rats

In a 3-month repeat dose study in rats, test article-related findings included abnormalities in long bone physis (growth plate) including increased physis thickness in all male rats administered 1000 mg/kg MOV, and increased epiphysis cartilage thickness in all female rats administered 1000 mg/kg MOV and all male rats administered 500 or 1000 mg/kg MOV. Changes to cartilage associated with the trachea were noted in male rats administered 500 (6/10) or 1000 (10/10) mg/kg MOV. Growth plate-related bone and/or cartilage findings were noted at systemic exposures approximately 5-fold higher (males) and 9-fold higher (females) than the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0-24hr} = 75.6 \text{ hr} \cdot \mu\text{M}$). The no-observed adverse effect level (NOAEL) was not defined (i.e., <150 mg/kg) for males due to weight loss at the lowest dose and was defined as 200 mg/kg/day for females.

Mild to marked increased thickness of the physis of the long bones (femur and tibia) of male rats dosed at 1000 mg/kg/day was characterized by irregularly widened physis involving the zone of hypertrophic chondrocytes, and occasional disruption of the physis. According to the study pathologist, histomorphologic features of the changes observed in the bone were indicative of an alteration in the normal physiologic progression of hypertrophic chondrocytes toward osteogenesis, resulting in impaired transformation of cartilage into new bone (endochondral ossification).

Eosinophilic cytoplasmic alteration of the chondrocytes in the cartilage of the trachea was noted in male rats administered 500 and 1000 mg/kg/day. This change did not impact the overall structure or integrity of the cartilage and did not cause airway restriction.

There were no findings in a 28-day repeat dose study in rats at similar systemic exposures (systemic exposures approximately 5-fold higher (males) and 9-fold higher (females) than the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0-24hr} = 75.6 \text{ hr} \cdot \mu\text{M}$)). This apparent discrepancy between the 28-day and 3-month repeat dose study may be related to the age of animals at the on-set of dosing. In the 28-day study rats were 8 to 9 weeks old at the start compared with 5 weeks of age at the start of the 3-month study.

Bone Effects in Rat and Rabbit Fetuses

MOV was administered orally to pregnant rats at 200, 500, and 1000 mg/kg/day from gestation days (GDs) 6 to 17 in a preliminary embryo-fetal development study. There were MOV-related skeletal malformations, variations, and delays in ossification at 1000 mg/kg/day.

In an embryo-fetal development study in rabbits, MOV was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Incomplete caudal vertebra and metacarpal ossification appeared to occur more at 400 mg/kg (9% of litters) and 750 mg/kg (6%) than in controls (2%). Although the incidence does not appear to increase with dose, this finding is noteworthy given the effects on bone and cartilage described previously in rats. Systemic exposures in pregnant rabbits at 400 and 750 mg/kg were approximately 6 and 18 times the mean clinical NHC exposure.

Conclusions

As previously described, animal studies suggest that MOV may affect bone and cartilage growth.

COVID-19 is typically associated with a mild disease course in most pediatric patients. REGEN-COV and sotrovimab mAb regimens are authorized for the treatment of mild-to-moderate COVID-19 in adolescents (patients 12 years of age and older weighing at least 40 kg) and bamlanivimab and etesevimab also includes authorized use in pediatric patients, including neonates. A juvenile toxicity study in rats is planned to further inform the safety of MOV in pediatric patients and a draft report is expected around March 2022.

Therefore, MOV should not be authorized at this time for use in patients less than 18 years old. This will be conveyed to prescribers through a Limitation of Authorized use and a Warning and Precaution in the health care provider fact sheet.

This topic was not an area of discussion during the November 30, 2021, Advisory Committee meeting, although one Committee member made the point that in females the growth plate closes by age 16 and in many males the growth plate is closed before age 18.

In addition, the above-described bone and cartilage toxicity may also be relevant to lactating women and nursing infants potentially exposed to NHC. There are currently no data on the presence of MOV or its metabolites in human milk. However, NHC was detected in the plasma of nursing pups from lactating rats administered MOV. Based on these available data, breastfeeding is not recommended during the treatment with MOV and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 4 days after the last dose. These recommendations should be included in the health care provider and patient fact sheets.

SEE ATTACHED ADDENDUM

4.3. Key Review Issue #3: Reproductive Toxicology Findings

Background

Nonclinical reproductive toxicology studies available for review include fertility studies in male and female rats, preliminary and pivotal EFD studies in rats and rabbits, and a pre- and postnatal development (PPND) study in rats.

In a preliminary EFD study in rats, the high dose was associated with reduced fetal body weight and an increase in post implantation loss, as well as external, visceral, and skeletal malformations. Systemic exposures (AUC) of NHC were approximately 8-fold the mean clinical NHC exposure. In the pivotal study, findings were limited to reduced fetal growth at systemic exposures approximately 3-fold the mean clinical NHC exposure.

There were no findings in a PPND study in rats (audited draft report). Notably, in the high dose group the mean maternal exposures to NHC were only 1.5-fold the mean clinical NHC

exposure, significantly lower than 8-fold the clinical NHC exposures which resulted in embryo-fetal toxicity noted in the EFD study. In the PPND draft report, low concentrations of NHC, 0.09% of maternal exposures, were measured in 10-day old pups, suggesting that NHC is present in breast milk.

Due to the embryo-fetal toxicity and bone and cartilage development findings in vivo, the lower exposures tested in the PPND study, and the lack of a completed juvenile toxicology study, there are both known and possibly unknown risks for use of MOV in pregnant or lactating individuals and pediatric patients.

Assessment

Fertility Studies (Male and Female Rats)

No effects of treatment were noted on fertility parameters. Based on the lack of findings the no observed effect level (NOEL) for fertility parameters was defined as ≥ 500 mg/kg in males and females. Systemic exposures (AUC) of NHC at the NOEL were approximately 2 times and 6 times the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0-24hr} = 75.6$ hr $\cdot\mu$ M) in males and females, respectively.

In the 3-month rat study, minimal degeneration of spermatogenic epithelium in two of 10 males administered 1000 mg/kg (high dose) was (1) characterized by segmental epithelial degeneration of isolated seminiferous tubules and spermatid retention, (2) associated with minimally increased cellular debris in the lumen of the epididymis, and (3) attributed to decreased body weight gain. At the end of the study, the decreases in males' body weight gain were -13%, -25%, and -55%, at low dose, mid dose, and high dose, respectively. The histomorphologic features of the testis were consistent with findings that have been described in rats with significant body weight suppression.

Embryo-Fetal Development (EFD) Studies

Rat

Note: In a preliminary EFD study female rats were administered doses up to 1000 mg/kg (NOAEL not defined as the study was preliminary). Findings from that study are included below. In the pivotal study rats were administered doses up to 500 mg/kg. In that study, findings were limited to reduced fetal growth at systemic exposures approximately 3 times the mean clinical NHC exposure at 800 mg Q12H (NOAEL 250 mg/kg based on maternal and developmental findings; exposures were approximately equivalent to the mean clinical NHC exposure at 800 mg Q12H).

Key study findings (from preliminary/range findings EFD study)

The 1000 mg/kg dose was also associated with reduced fetal body weight and an increase in post-implantation loss, as well as external, visceral, and skeletal malformations in surviving fetuses. Administration of 1000 mg/kg to pregnant rats from GDs 6 to 17 caused a transient decrease in food consumption between GDs 6 and 8 and an associated reduction in body weight between GDs 8 and 12.

Systemic exposures (AUC) of NHC were: at 100 mg/kg: 22.5 hr $\cdot\mu$ M; at 200 mg/kg: 45.7 hr $\cdot\mu$ M; at 500 mg/kg: 217 hr $\cdot\mu$ M; and at 1000 mg/kg: 570 hr $\cdot\mu$ M, approximately 0.3, 0.6, 3, and 8 times the mean clinical NHC exposure at 800 mg Q12H ($AUC_{0-24hr} = 75.6$ hr $\cdot\mu$ M).

External malformations

There were MOV-related fetal external malformations of the eyes (small or absent eye bulge) at 1000 mg/kg/day (three fetuses from two litters, compared to none in controls).

Visceral malformations

At 1000 mg/kg/day, there were MOV-related fetal visceral malformations (absent kidney in two fetuses from two litters, compared to none in controls). There was one fetus in the 1000 mg/kg/day group with multiple cardiovascular and associated observations (ventricular septal defect, dilated pulmonary trunk, narrowed aortic arch, malpositioned aorta, large ventricle, and fluid-filled thoracic cavity). This fetus was also observed to have local edema at external examination. Because this was a singular occurrence and ventricular septal defect with similar associated abnormalities has been observed in vehicle controls in this laboratory, the abnormalities in this fetus were considered by the study director to be incidental and unrelated to MK-4482 treatment.

Skeletal malformations

Consistent with the external malformation (small or absent eye bulge), there were MOV-related fetal coronal malformations at 1000 mg/kg/day (small or absent eye in four fetuses from three litters, compared to none in controls).

There were MOV-related skeletal malformations, variations, and delays in ossification at 1000 mg/kg/day. Specifically, there were increased incidences of rib malformations (primarily detached ribs), thoracic vertebra malformation, lumbar vertebra malformation, skull malformation, cervical ribs, trace supernumerary ribs, and incomplete ossification of thoracic vertebrae and/or sternbrae. The skull malformation observed in one fetus was a small eye socket (reduced spacing between the right frontal bone and zygomatic bone), presumably representing a small eye that was not observed at external examination. In addition, the mean number of ossified sacrocaudal vertebrae was reduced.

The incidences of cervical ribs in the 200 and 500 mg/kg/day dose groups were higher than in concurrent controls (five fetuses in two litters [litter means 4.8%] and five fetuses in three litters [litter mean 6.3%], respectively, versus two fetuses in two litters [litter mean 2.4%]).

PPND study findings

MOV was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the recommended human dose) from GD 6 through lactation Day 20. No effects were observed in offspring. Low concentrations to NHC, 0.09% of maternal exposures, were measured in 10-day old pups, suggesting that NHC is present in breast milk.

Rabbit

Key study findings

Developmental toxicity included reduced fetal body weights at 750 mg/kg/day. Incomplete ossification in fetuses from rabbits administered 400 and 750 mg/kg MOV may be test article-related. Incomplete ossification (specifically caudal vertebra and metacarpal) appeared to occur more at 400 mg/kg (9% of litters) and 750 mg/kg (6%) than in controls (2%) and is noteworthy given effects on bone and cartilage seen in rats. The Sponsor concluded that these changes were not related to test article due to the lack of dose dependency and the fact that the values were within or just outside the historical ranges.

Administration of 125 mg/kg, 400 mg/kg, and 750 mg/kg to pregnant rabbits on GD 7 through 15 resulted in systemic exposures (AUC_{0-24hr}) of 111 hr* μ M, 490 hr* μ M, and 1360 hr* μ M, respectively. The mean clinical NHC exposure at 800 mg Q12H was 75.6 μ M*hr. The NOEL was defined as 125 mg/kg based on maternal and developmental toxicity.

Conclusions

Use in Pregnancy

Given the nonclinical findings of embryo-fetal toxicity, MOV is not recommended for use during pregnancy. There are alternative authorized therapies available for the treatment of mild-to-moderate COVID-19 that do not have an embryo-fetal toxicity safety signal. However, MOV may be used during pregnancy in certain situations if the risk benefit assessment is favorable to the individual patient. If MOV is used during pregnancy, prescribing health care providers must communicate the known and potential benefits and the potential risks of using MOV during pregnancy to the patient as outlined in the Fact Sheet for Health Care Providers in Warnings and Precautions (Sections 5.1, 5.2), Use in Specific Populations (Sections 8.1, 8.3), and Nonclinical Toxicology (Section 13.1). Further, the prescriber must document that the known and potential benefits and the potential risks of MOV use during pregnancy, as outlined in the Fact Sheet for Patients and Caregivers, were discussed with the patient.

Finally, the prescribing health care provider must inform pregnant individuals of the Sponsor's pregnancy surveillance program. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing health care provider to disclose patient specific information to the Sponsor, the prescribing health care provider must provide the patient's name and contact information to the Sponsor. A toll-free number and web address will be provided in the fact sheets for health care providers and patients to report exposures.

The nonclinical embryo-fetal toxicity findings, and the use of MOV during pregnancy, were concerning to Committee members at the November 30, 2021, Advisory Committee meeting. In general, members voting "Yes" advised that MOV not be used during pregnancy, or be used only under certain situations, and after health care provider and patient discussions regarding the potential risks to the fetus. The Advisory Committee discussions were taken under consideration when formulating the recommendations for use during pregnancy as stated above.

Use in Individuals of Childbearing Potential

Regarding use in individuals of childbearing potential, given that MOV is associated with clinical benefit in high-risk adults with mild-to-moderate COVID-19, withholding MOV from individuals of childbearing potential for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate, is not justified.

It is important to minimize the risk of an individual who is unaware that they are pregnant inadvertently exposing a fetus to MOV. Therefore, unless an individual has undergone permanent sterilization, is currently using an intrauterine system or contraceptive implant, or is someone in whom pregnancy is not possible, a prescribing health care provider must assess whether an individual of childbearing potential is pregnant or not. This assessment can be based on the first day of the last menstrual period in individuals who have regular menstrual cycles, are using a reliable method of contraception correctly and consistently or have had a negative pregnancy test.

A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly or consistently. Pregnancy testing will not be required for all individuals of childbearing potential as this is thought to be infeasible under the framework of an EUA and as there is a precedent for allowing drugs with evidence of embryofetal toxicity in animals but not humans to be prescribed without requiring documentation of a negative pregnancy test.

The above recommendations were discussed and agreed by the Division of Pediatric and Maternal Health and Division of Urology, Obstetrics, and Gynecology.

To further minimize the risk of embryofetal toxicity among individuals of childbearing potential, a reliable method of contraception used correctly and consistently is recommended during the 5-day treatment period and for 4 days after the last dose of MOV.

Lastly, prescribing health care provider must communicate to individuals of childbearing potential that a pregnancy surveillance program is available to monitor pregnancy outcomes in those exposed to MOV during pregnancy.

Pregnancy Surveillance Program

As described above, the Sponsor has created a pregnancy surveillance program to collect information on pregnancy outcomes in individuals who are exposed to MOV during pregnancy. A toll-free number and web address will be provided in the fact sheets for health care providers to report exposures. Under the authorization, prescribers will be required to report all known MOV exposures during pregnancy, providing the pregnant patient agrees to participate in the registry and allows the prescribing health care provider to disclose patient specific information to Merck. As the prescribing health care provider may not have ongoing involvement in the patient's care, they will be asked to provide the Sponsor with the patient's name and contact information. The Sponsor will then be required to exercise due diligence to capture pregnancy outcomes data. The outcomes data that the Sponsor intends to collect were reviewed by the Division of Antivirals and by the Division of Pediatric and Maternal Health and are considered acceptable. The Sponsor will be required to submit a monthly report summarizing pregnancy exposures and outcomes to the Division of Antivirals.

The review team acknowledges that it will be challenging to capture pregnancy exposures and pregnancy outcomes from patients who are not known to be pregnant at the time MOV is prescribed. If MOV is prescribed by a health care provider with whom the patient has a one-time encounter (e.g., an emergency room or urgent care provider), it is not reasonable to expect the prescriber to become aware of the pregnancy exposure or to report the pregnancy exposure and outcomes. To increase the likelihood of capturing these exposures, prescribers will be required to communicate to all nonpregnant individuals of childbearing potential that a pregnancy surveillance program is available to monitor pregnancy outcomes in those exposed to MOV during pregnancy and to encourage the patient to participate in the pregnancy surveillance program should they become pregnant within 6 weeks of taking MOV.

Dear Health Care Provider Letter

To further inform prescribing health care providers and treating health care providers of the many unique considerations regarding MOV use in pregnancy and in individuals of childbearing potential, a Dear Health Care Provider letter will be widely distributed by the Sponsor. This letter will also provide information about the pregnancy surveillance program and it is hoped that this will help improve reporting rates.

4.4. Key Review Issue #4: Effect of MOV on SARS-CoV-2 Spike Protein Sequences in Clinical Trials

Background

MOV inhibits SARS-CoV-2 replication by causing the accumulation of nucleotide changes in viral RNA which ultimately render viral populations less fit or unviable (for further details, see Section [XIII.1](#) “Mechanism of Action”). In theory, the random viral RNA mutagenic effects of MOV treatment could result in genetic changes anywhere in the viral genome, which under certain conditions could impact viral susceptibility to other antiviral agents or to the host immune response. Of particular importance, amino acid changes in the viral spike protein could contribute to reduced viral susceptibility to the host antibody response or to spike protein targeting monoclonal antibody therapeutics.

This section summarizes analyses conducted by the Sponsor and FDA to characterize MOV treatment-emergent changes in the SARS-CoV-2 spike protein sequences in clinical trials (1) to confirm the mechanism of MOV action leading to accumulation of nucleotide changes in the SARS-CoV-2 genome, and (2) to determine if MOV treatment causes changes in the viral spike protein that could facilitate SARS-CoV-2 evolution or immune escape.

Assessment

SARS-CoV-2 Sequence Analysis Methods

Viral next generation sequencing (NGS) analyses from MOV clinical trials were conducted in a central laboratory, and detailed methods are described in an NGS assay validation report and a nonclinical information amendment (SDN 10). Briefly, viral RNA samples from NP and oropharyngeal (OP) swabs with sufficient RNA levels to meet quality control criteria (defined as >22,000 copies/mL) were subjected to reverse-transcriptase polymerase chain reaction amplification and full genome sequencing using the Ion Torrent NGS platform. The Ion AmpliSeq SARS-CoV-2 Research panel consists of two primer pair pools that target 237 amplicons (both strands sequenced) specific to the SARS-CoV-2 virus and five human expression controls.

According to the Sponsor, this panel, with an amplicon length range of 125 to 275 bp, provides >99% coverage of the SARS-CoV-2 genome. A variant frequency cutoff was not used but most reported variant frequencies were >2%. Variants were reported relative to the prototypic reference isolate, Wuhan-Hu-1 (GenBank:MN908947.3). Nucleotide mutation rates were defined as the number of nucleotide changes observed in postbaseline samples compared with the baseline sequence per 10,000 bases across the entire viral genome (~30,000 bases).

The NGS data from MK-4482-002, Part 1 and MK-4482-001 were submitted both in raw format (.fastq files) and also in .xpt STDM and an analysis-ready ADaM-like format. Independent FDA analyses of the .xpt files were conducted to characterize treatment-emergent amino acid changes in MOV- and placebo-treated participants in these trials. Treatment-emergent amino acid changes (i.e., detected in postbaseline samples but not baseline samples, regardless of NP/OP sample type) based on a variant sensitivity threshold of 5% were identified in the viral spike sequences and compared between MOV- and placebo-treated participants. Raw NGS fastq data from a subset of participants were also independently analyzed to confirm/corroborate the analyses of the .xpt data.

For MK-4482-002, Part 2, limited SARS-CoV-2 sequence analysis data were reported at the time of this review, so the treatment-emergent amino acid analyses focused primarily on MK-4482-002, Part 1 (outpatient population/Phase 2) and MK-4482-001 (hospitalized population/Phase 2).

Analysis of SARS-CoV-2 RNA Mutation Rates: MK-4482-002, Part 2

Based on available data from a small subset of participants (12%, 92/762), and consistent with the MOV mechanism of action, MOV treatment was associated with a modest but significantly higher nucleotide mutation rate in SARS-CoV-2 populations in NP swab samples collected on Day 5 (EOT) ([Table 26](#)).

Table 26. SARS-CoV-2 RNA Mutation Rate (Number of Nucleotide Changes/10,000 Nucleotides Sequenced Across Entire Genome), MK-4482-002, Part 2

Visit	Analysis Parameter	MK-4482 800 mg				Placebo				P-Value MOV vs. PBO ^a
		N	Median	Min	Max	N	Median	Min	Max	
Baseline	Number of SARS-CoV-2 Mutations Relative to Reference (NP Swab)	42	13.0	8.7	19.7	50	12.7	9.7	15.7	0.272
Day 5 (EOT)	Number of SARS-CoV-2 Mutations Relative to Baseline (NP Swab)	42	2.5	0.0	46.3	50	1.3	0.0	30.0	0.005

Source: FDA analysis of Sponsor-related mutation rates

^a Wilcoxon test

Abbreviations: EOT, end of treatment; MOV, molnupiravir; N, number of participants; NP, nasopharyngeal; PBO, placebo; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Analyses conducted by the Sponsor indicate most of the nucleotide mutations observed were cytidine (C) ↔ uridine (U) and guanosine (G) ↔ adenosine (A) transition mutations, again consistent with the MOV mechanism of action, although MOV treatment was associated with increases in all types of analyzed nucleotide changes ([Table 27](#)).

Table 27. Mean Numbers of SARS-CoV-2 RNA Transition, Transversion and Other Nucleotide Changes Relative to Baseline, MK-4482-002, Part 2

Treatment	N	Transitions				Transversions								Other (In/Del)
		C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C	A:C	A:U	
MOV	42	6.6	1.8	3.6	2.2	0.2	0.1	0.1	0.2	1.6	0.1	0.2	0.4	1.7
Placebo	50	4.1	1.1	0.4	0.5	0.1	0.0	0.0	0.0	1.0	0.0	0.1	0.2	1.2

Source: adapted from p002v02eff, pg. 153

Abbreviations: A, adenosine; C, cytidine; Del, deletion; In, insertion; G, guanosine; MOV, molnupiravir; N, number of participants; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U, uridine

Analysis of SARS-CoV-2 RNA Mutation Rates: MK-4482-002, Part 1 and MK-4482-001

Consistent with the results from MK-4482-002, Part 2, MOV treatment in MK-4482-002, Part 1 was associated with a higher rate of detected nucleotide changes in postbaseline viral genomes in NP swab samples ([Table 28](#)). Again, most of the nucleotide mutations observed were C↔U and G↔A transition mutations, although MOV treatment was associated with increases in all types of analyzed nucleotide changes ([Table 29](#)).

Table 28. Numbers of SARS-CoV-2 Nucleotide Changes Relative to Baseline per 10,000 Bases Analyzed, NP Swab Samples, MK-4482-002, Part 1

Visit	MK-4482 200 mg		MK-4482 400 mg		MK-4482 800 mg		Placebo	
	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)
SARS-CoV-2 RNA Mutation Rate (per 10,000 bases)								
Day 3	29	4.4 (13.95)	32	6.1 (23.90)	27	2.4 (3.29)	29	0.9 (0.51)
EOT (Day 5)	14	7.9 (14.60)	15	6.7 (7.83)	11	8.7 (8.38)	15	2.0 (3.39)
Maximum at Day 3 or EOT (Day 5)	30	7.6 (16.52)	32	8.5 (24.13)	27	5.6 (6.56)	31	1.5 (2.40)

SD=Standard deviation.
N=Number of participants with baseline and at least one postbaseline test result in the specified analysis window.
The mutation rate is calculated as number of nucleotide mutations compared to the baseline sequence per 10,000 bases across the entire viral genome (30,000 bases).
Day 3 includes post-baseline records up to day 4 relative to randomization. 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.

Source: Sponsor's analysis, Part 1 CSR pg. 183

Abbreviations: EOT, end of treatment; NP, nasopharyngeal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 29. Mean Numbers of Types of SARS-CoV-2 Nucleotide Changes Relative to Baseline, NP Swab Samples, MK-4482-002, Part 1

Visit	Treatment	N	Transitions				Transversions						Other Nucleotide Changes		
			C:U	U:C	G:A	A:G	C:A	C:G	U:A	U:G	G:U	G:C		A:C	A:U
Day 3	MK-4482 200 mg	33	4.5	1.5	1.0	0.7	0.1	0.0	0.0	0.0	1.4	0.1	0.1	0.2	1.2
	MK-4482 400 mg	35	6.3	2.6	0.7	0.5	0.0	0.1	0.0	0.1	2.6	0.2	0.2	0.2	1.9
	MK-4482 800 mg	31	2.2	0.4	1.5	0.5	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.6
	Placebo	32	1.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.4
EOT (Day 5)	MK-4482 200 mg	19	7.3	2.1	2.1	1.1	0.0	0.1	0.0	0.0	2.6	0.2	0.2	0.5	1.5
	MK-4482 400 mg	17	6.4	1.4	4.2	2.2	0.1	0.0	0.0	0.1	0.5	0.1	0.0	0.2	0.8
	MK-4482 800 mg	14	9.0	2.5	5.7	2.6	0.0	0.0	0.0	0.1	0.9	0.0	0.0	0.0	1.1
	Placebo	20	2.6	0.2	0.2	0.3	0.1	0.0	0.0	0.0	0.5	0.1	0.1	0.1	0.6

N = number of participants with both baseline and post-baseline SARS-CoV-2 gene sequencing data at the reported visit.

Source: Sponsor's analysis, p002vrv01vir, pg. 6

Abbreviations: A, adenosine, C, cytidine; EOT, end of treatment; G, guanosine; NP, nasopharyngeal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; U, uridine

The Sponsor conducted additional analyses of SARS-CoV-2 nucleotide mutation rates focusing on all minor nucleotide variants detected at frequencies of 0.4 to 10%. These analyses similarly detected a higher frequency of nucleotide mutations in MOV- versus placebo-treated participants. Statistical analyses conducted by the Sponsor indicated a linear MOV dose-response relationship in the numbers of minor nucleotide variants detected, and this relationship remained when controlling for viral RNA levels in samples.

In MK-4482-001, consistent with the results from MK-4482-002, Parts 1 and 2, a modest increase in overall SARS-CoV-2 mutation rate was detected in NP swab viral RNA samples in MOV-treated participants compared to placebo-treated participants. A clearer MOV dose-response relationship in viral mutation rate in NP samples was again observed when analyses were restricted to minor nucleotide variants detected at frequencies of 0.4 to 10%.

Analysis of Spike Treatment-Emergent Amino Acid Changes: MK-4482-002, Part 1

Results for all three MOV arms in MK-4482-002, Part 1 were pooled for analyses of treatment-emergent amino acid changes in the spike protein. Specific amino acid changes or nucleotide structural mutations detected at the same amino acid position in \geq two participants (pooled MOV- and placebo-treated) were identified and tabulated. The NGS analyses were generally restricted to samples collected through Day 5 (EOT), so these analyses would not identify changes that emerged or persisted at later timepoints.

Results of these analyses are summarized in [Table 30](#). Consistent with the MOV mechanism of action, a greater proportion of participants in the MOV arms relative to the placebo arm had at least one treatment-emergent amino acid substitution or other structural nucleotide change (deletion, insertion) detected in the spike gene, and amino acid changes were scattered throughout the coding sequence. A total of 81 emergent spike substitutions/changes were detected among 38 MOV-treated participants and nine placebo-treated participants. Each of the nine placebo-treated participants had one treatment-emergent spike amino acid substitution detected, while a total of 72 substitutions were detected in the 38 MOV-treated participants (median one substitution per participant, range 1–7). Amino acid changes, including substitutions, insertions, or deletions, were detected in multiple participants at several spike amino acid positions, mostly in MOV-treated participants.

Table 30. Treatment-Emergent Amino Acid Changes (Through Day 5/EOT) Detected at ≥5% Frequency in Spike Sequences, MK-4482-002, Part 1

AA Change	# Participants in MOV Arms (Pooled, n=113)	# Participants in Placebo Arm (n=39)
Any treatment-emergent spike AA change	38 (34%)	9 (23%)
Total number of AA changes	72	9
Total number of AA changes per participant	1-7 per participant (18 with ≥2 changes)	1 per participant
AA positions with ≥2 participants with change		
NTD aa 139-145	5	0
ΔP139-Y145	1 ^a	
P139S	1 ^a	
ΔL141-Y144	1 ^a	
ΔL141-Y144, Fins	1 ^a	
ΔY145	1 ^a	
G261I/V	2	0
S297L	1	1
T385I	2	0
E484K	2	0
P681H	2	0
S884F	1	1
A1022T	2	0

Source: FDA analysis

^a Each of these is detected in a separate participant at variant frequencies of ~6 to 20%

Abbreviations: AA, amino acid; EOT, end of treatment; MOV, molnupiravir

Of particular interest, in multiple participants MOV treatment was associated with amino acid changes at sites/regions of the spike protein that are likely under immune or other evolutionary selective pressure. Amino acid changes at these sites are found in some SARS-CoV-2 variants of public health importance (e.g., see (Plante et al. 2021) for review; (Stanford 2021)). Our analyses identified or confirmed the following:

- Five MOV-treated participants (0 placebo-treated participants) had treatment-emergent amino acid substitutions, insertions, or deletions in the region of amino acids P139-Y145 in the N-terminal domain (NTD). This is an exposed region of the spike protein that is believed to be under strong antibody selective pressure (Harvey et al. 2021), and deletions or substitutions in this region are found in several important SARS-CoV-2 variants.

- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent E484K, which is a key receptor-binding motif substitution associated with neutralizing antibody escape and is present in several important SARS-CoV-2 variants.
- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent P681H, which is adjacent to the spike furin cleavage site and is present in multiple SARS-CoV-2 variants, and is in the same position where a P681R substitution has been hypothesized to enhance infectivity of the Delta variant (Liu et al. 2021).

Importantly, analyses of raw NGS data from the participants with the noted NTD changes confirmed the analyses of the .xpt analysis datasets. For example, while the ION Torrent NGS platform is prone to reporting single base insertion or deletion artifacts in homopolymeric sequence reads, the NGS reads in these NTD regions were generally of high quality and clearly indicated deletions of stretches of amino acid codons (i.e., multiples of 3, up to 21 nt).

Analysis of Spike Treatment-Emergent Amino Acid Changes: MK-4482-001

Similar analyses of SARS-CoV-2 spike sequence were conducted for the clinical trial MK-4482-001 (hospitalized population) ([Table 31](#)). Consistent with the MOV mechanism of action and the results from MK-4482-002, Part 1, participants treated with MOV in MK-4482-001 were more likely to have at least one detected treatment-emergent spike amino acid change, compared with those treated with placebo. Again, some notable observations include the following:

- Five MOV-treated participants (one placebo-treated participant) had treatment-emergent amino acid substitutions or deletions in the region of amino acids P139-Y145 in the NTD.
- Two MOV-treated participants (0 placebo-treated participants) had treatment-emergent P681H, adjacent to the spike furin cleavage site.
- One MOV-treated participant (0 placebo-treated participants) had treatment-emergent N501Y, which is another important spike change that contributes to neutralizing antibody escape and virus attachment.

The treatment-emergent changes noted above were detected in six (7%) MOV-treated participants and one (4%) placebo-treated participant. Three of these changes were detected in one MOV-treated participant, and in a large fraction of sequences (32 to 77%): Δ Y145, N501Y, and P681H. This same participant had several other treatment-emergent amino acid changes in the spike protein and elsewhere in the genome, and the Sponsor reported that the viral clade designation changed for this participant between baseline and Day 3, so it is unclear if this reflects extensive MOV-associated mutagenicity, coinfection with another SARS-CoV-2 variant, or a technical issue. All of the other changes were detected in separate participants at relatively lower variant frequencies (5 to 12%).

Table 31. Treatment-Emergent Amino Acid Changes Detected at ≥5% Frequency in Spike Sequences, MK-4482-001, Part 1

AA Change	# Participants in MOV Arms (Pooled, n=89)	# Participants in Placebo Arm (n=27)
Any treatment-emergent spike AA change	31 (35%)	5 (19%)
AA positions with ≥2 participants with change		
del_L141-Y144	2	0
G142V	1	0
ΔY145	2	1
A262S	1	1
N501Y	1 ^a	0
P681H	2	0

Source: FDA analysis

^a Treatment-emergent only in one participant but noted because it is associated with reduced susceptibility to some monoclonal antibodies.

Abbreviations: AA, amino acid; MOV, molnupiravir

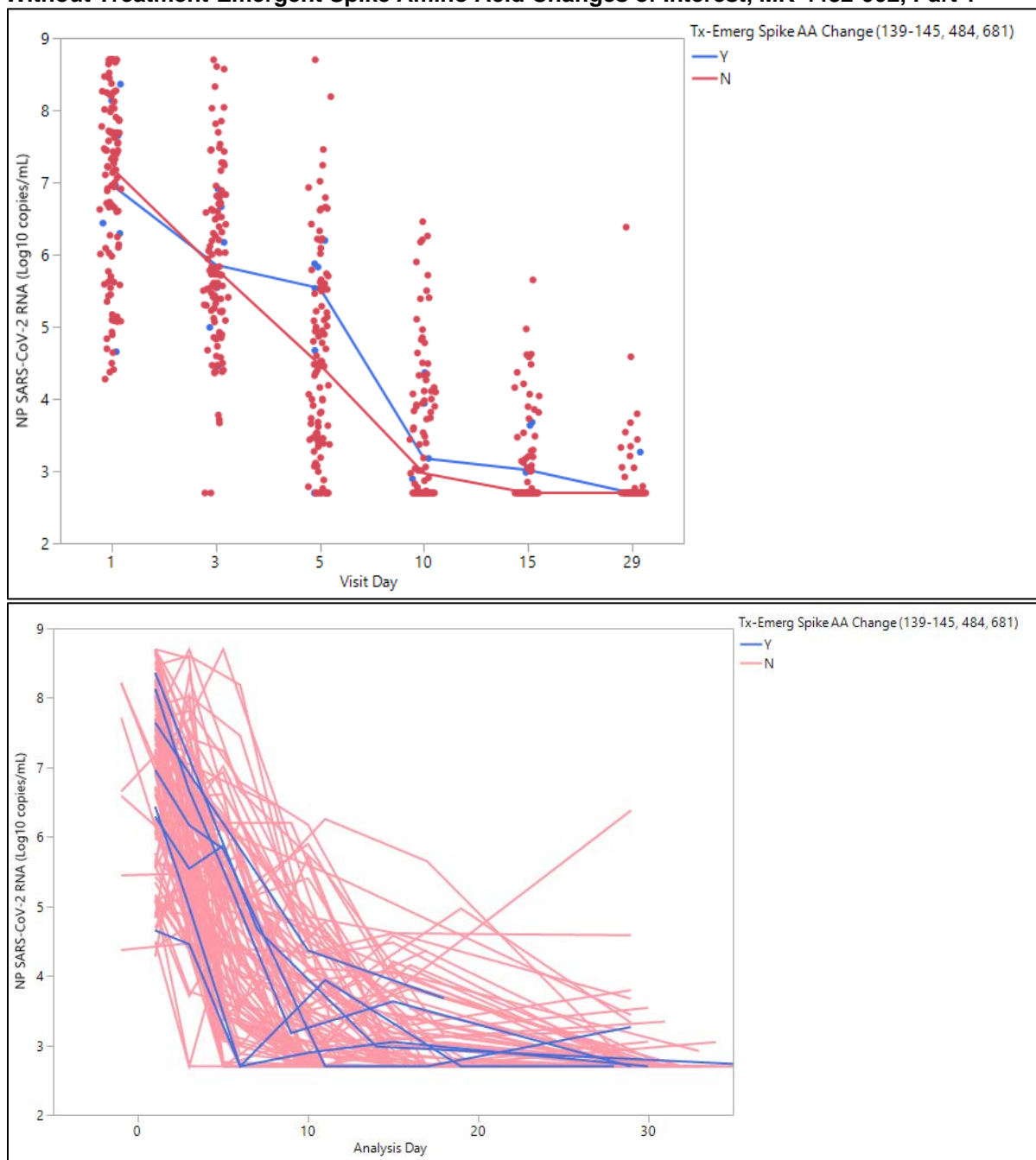
Analyses To Explore Potential Clinical Relevance of Detected Spike Treatment-Emergent Amino Acid Changes

Additional analyses from MK-4482-002, Part 1 were conducted to explore the potential clinical impact of the MOV treatment-emergent changes in the spike protein, focusing particularly on the NTD changes and deletions of amino acids 139 to 145, and substitutions E484K and P681H. A total of seven (6%) MOV-treated participants had these treatment-emergent changes in the spike protein. Two participants had two of these changes detected: P139S+P681H and ΔP139-Y145+P681H. In all seven participants, these spike changes of interest were detected as minority variants comprising 5 to 20% of the viral RNA population.

These seven participants represent only a subset of the spike amino acid changes detected in MOV- or placebo-treated participants, and several other emergent amino acid changes were detected in MOV- and/or placebo-treated participants at positions of unknown significance throughout the spike protein. Five of the seven participants tested negative for anti-SARS-CoV-2 antibody at baseline, while results were not reported for the other two participants.

As shown in [Figure 5](#), participants with the key spike amino acid changes of interest (changes in amino acids 139 to 145, E484K and P681H) had a shallower median decline in viral RNA levels in NP swab samples between the Day 3 and Day 5 (EOT) visits. However, this difference was transient, and it is unclear if this reflects a true difference or if this is attributed to the small sample size in the spike amino acid change group, as results for all individual participants show substantial variability in these results.

Figure 5. Viral RNA Levels in NP Swabs in MOV-Treated Participants Among Those With or Without Treatment-Emergent Spike Amino Acid Changes of Interest, MK-4482-002, Part 1



Source: FDA analysis

Note: Viral RNA shedding data are not shown for placebo-treated participants or participants without available sequence analysis data. Treatment-emergent spike amino acid changes were identified in samples collected on Day 3 or Day 5 (EOT); sequence analysis data are not available for later timepoints. Trendline in top panel shows median values. The bottom panel shows results for individual participants.

Abbreviations: AA, amino acid; MOV, molnupiravir; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

There was no evidence that the emergence of these spike protein amino acid changes affected the levels of cell culture infectious virus in NP or OP specimens, although it should be noted that culturable virus was rarely detected across the entire study population (~10 to 20% at baseline, 0 to 4% postbaseline, NP samples). Of the seven participants with the key spike changes of interest, only one participant had cell culture infectious virus detected in an NP or OP specimen, and it was a baseline sample.

Furthermore, there was no evidence that the emergence of these spike amino acid changes contributed to enhanced disease, at least based on the clinical endpoint of hospitalization or death. None of the seven participants noted above reached this endpoint through Day 29. In addition, there was no clear evidence that participants with any treatment-emergent spike change were more or less likely to reach the clinical endpoint, although the hospitalization rate was low overall in MK-4482-002, Part 1.

Other observations and considerations from these analyses include the following:

- While treatment-emergent spike protein amino acid changes appeared to be detected at a higher rate in MOV-treated participants, it should be recognized that treatment-emergent spike amino acid changes were also observed in some participants treated with placebo, consistent with this being a protein under natural evolutionary pressure.
- A majority of the spike protein amino acid changes were detected as minority variants. Considering all of the 72 treatment-emergent spike amino acid changes detected in MOV-treated participants in MK-4482-002, Part 1, 56 (78%) of these changes were detected in <15% of the sequence population.
- Consistent with most changes occurring as minority variants, when sequence data were available for multiple postbaseline samples (NP or OP swabs, Day 3 or Day 5/EOT), the treatment-emergent spike amino acid changes were detected only in one sample, indicating compartmentalized or transient detection of these changes. Note that 38% (57/152) of participants in the MK-4482-002, Part 1 dataset had data from only a single postbaseline sample.
- Transition mutations are the types of mutations most often enriched by MOV and directly tied to its mechanism of action, but the types of nucleotide changes leading to the observed amino acid changes in spike were not all transition mutations. Other nucleotide changes leading to spike amino acid changes in these datasets included transversions, deletions and insertions. However, MOV (or more specifically, NHC-triphosphate) apparently can increase the rate of other types of nucleotide changes detected in clinical viral specimens. Also, in theory, some changes such as deletions could arise from error repair mechanisms. In any case, any uncommon types of nucleotide changes could become enriched in the viral population if they confer a selective advantage.
- In a few individual participants, numerous treatment-emergent spike changes were detected in association with other changes elsewhere in the genome, as noted above for the MK-4482-001 participant with treatment-emergent $\Delta Y145$, N501Y, and P681H. It is unclear if this reflects extensive MOV-driven mutagenesis and selection, coinfection with multiple SARS-CoV-2 variants, or a technical issue.

Conclusion

Collectively, these analyses indicate MOV treatment may increase the rate of emergence of SARS-CoV-2 populations with amino acid changes in the viral spike protein, consistent with its

mutagenic mechanism of action. However, there remain many uncertainties regarding these findings and their clinical and public health implications.

At the individual patient level, there was no evidence that the emergence of spike amino acid changes affected virologic or clinical outcomes in outpatients with COVID-19 in MK-4482-002, Part 1. However, the Division recognizes that the available data are limited, and in theory, MOV treatment-emergent changes in spike (or in other immune or drug targets) could have different clinical implications in different patient populations.

It is challenging to predict the broader public health risk of MOV treatment-associated spike amino acid changes. The most concerning public health risk would be that MOV mutagenesis could contribute to the emergence of novel SARS-CoV-2 variants with important phenotypic properties, such as reduced susceptibility to antibody-based therapeutics or vaccine-induced immune responses.

On the other hand, on a per-patient basis the transmissibility of such variants is likely quite low. Most spike protein changes observed in MK-4482-002, Part 1 were detected as minority variants. Even in the absence of an antiviral effect, overall viral shedding levels will be declining rapidly by the time a MOV-associated spike amino acid variant emerges in treated outpatients with COVID-19. The antiviral activity of MOV, which is linked directly to its mutagenic activity, likely accelerates this viral clearance. Consistent with MOV accelerating clearance of replication competent, transmissible SARS-CoV-2, there is evidence from a nonclinical study in ferrets that MOV can reduce SARS-CoV-2 transmission to untreated contact animals (Cox et al. 2020). There was no clear evidence that emergence of spike protein amino acid changes in MK-4482-002, Part 1 was associated with a rebound in viral RNA shedding, and cell culture infectious virus was not detected in any MOV-treated participants by Day 5/EOT (and only in 4% of placebo-treated participants at Day 5).

It also has to be recognized that the SARS-CoV-2 spike protein acquires genetic changes frequently, regardless of any MOV mutagenic activity. In the placebo arm in MK-4482-002, Part 1, 23% of participants with available data had a detected treatment-emergent amino acid change in the spike protein. Natural immune responses and other beneficial treatments and vaccines can also influence SARS-CoV-2 evolution. Therefore, it is unclear to the Division if treatment of outpatients with COVID-19 with MOV would change current patterns and trajectories of SARS-CoV-2 evolution.

This topic was discussed extensively during the November 30, 2021, Advisory Committee meeting and mixed perspectives were expressed by the Committee members. Some members had major concerns about the potential for MOV-associated mutagenesis of the SARS-CoV-2 spike gene to facilitate SARS-CoV-2 evolution, while others seemed less concerned on the basis that MOV may not have a substantial impact on SARS-CoV-2 evolution that is already occurring naturally. One Committee member noted that the overall impact of MOV on SARS-CoV-2 spike protein evolution may be minimal given that selective pressures on the spike protein (which are not directly affected by MOV) are the primary driver of SARS-CoV-2 evolution, and the impact of a MOV-associated increase in SARS-CoV-2 mutation rate may be minimized by the beneficial effect of MOV in facilitating viral clearance.

Most Committee members agreed that additional studies are warranted to characterize this risk, particularly in MOV-treated immunocompromised patients. Furthermore, Committee members recommended steps should be taken to maximize viral clearance in MOV-treated patients and minimize any potential risk of developing and transmitting new SARS-CoV-2 variants, such as advising patients to complete the 5-day dosing regimen.

To provide more insight into the mechanisms and individual patient and public health risks of MOV-associated SARS-CoV-2 spike changes, the Division has requested that the Sponsor continue to collect, analyze, and report viral sequencing data from the full randomized population in MK-4482-002, Part 2. In addition, the Division is requesting that the Sponsor conduct SARS-CoV-2 cell culture infectivity assays for any MK-4482-002 clinical specimens in which encoded amino acid changes are detected in the viral spike gene. These analyses will include MOV-treated immunocompromised patients from MK-4482-002, Part 2.

As additional studies are conducted to further characterize the risk of MOV-associated SARS-CoV-2 evolution, this risk is mitigated, in part, by the restriction of the EUA to patients without other treatment options, which in effect minimizes unnecessary use of MOV. Also further mitigating this risk, the Fact Sheet for Health Care Providers includes language recommending that patients complete the full 5-day treatment course and remain physically isolated in accordance with public health recommendations, which are intended to maximize viral clearance and minimize any potential risk of developing and transmitting new SARS-CoV-2 variants.

In summary, the Division currently does not have major concerns about the potential for MOV to enrich for low level variants with spike protein amino acid changes within an individual treated patient. However, it remains unclear if the potential for MOV-associated changes in the SARS-CoV-2 spike protein presents a significant risk to public health, considering the potential for widespread use of MOV. The additional studies and recommendations noted above are intended to further characterize and mitigate this theoretical risk, and thus help to optimize the risk-benefit profile of MOV.

4.5. Key Review Issue #5: Analyses of Potential MOV Resistance or Remdesivir Cross-Resistance in Clinical Trials

Background

The mechanism of MOV anti-SARS-CoV-2 activity involves interactions between the active triphosphate (NHC-TP), the template, and the viral replicase complex, primarily the viral RNA-dependent RNA polymerase (RdRp, nonstructural protein 12 [nsp12]). The viral 3'-5'-exoribonuclease (ExoN, nsp14) could also play a role in the mechanism of action and antiviral activity of MOV, as this viral protein has proof-reading activity that can correct errors in the SARS-CoV-2 genome. Multiple other nonstructural viral proteins (nsp7–10) are cofactors in the viral replicase complex and thus could also interact directly or indirectly with NHC or its metabolites. In theory, the development of SARS-CoV-2 resistance to MOV could involve amino acid changes in any of these viral proteins. Coronavirus resistance selection studies in cell culture did not identify any clear MOV or NHC resistance-associated substitutions.

Remdesivir (Gilead 2020) is an approved SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Like MOV/NHC, the active triphosphate of remdesivir is a substrate of the viral RdRp (nsp12) and incorporates into viral RNA, although inhibition of viral replication is thought to occur primarily by RNA chain termination, not mutagenesis. Nevertheless, because both MOV and remdesivir interact with the viral RdRp, amino acid changes in RdRp associated with resistance to one drug could affect the antiviral activity of the other, referred to as cross-resistance. Amino acid changes in nsp12 reported to be potentially associated with reduced susceptibility or resistance to remdesivir

include F480L, D484Y, V557L, and E802A/D. None of these substitutions appeared to reduce NHC antiviral activity in cell culture using a SARS-CoV-2 replicon-based phenotypic assay.

This section summarizes analyses conducted by the Sponsor and FDA to characterize MOV treatment-emergent changes in the SARS-CoV-2 nsp12 and nsp14 in clinical trials to identify potential MOV resistance pathways, and to assess the potential for enrichment of viruses with cross-resistance to remdesivir.

Assessment

The same MK-4482-002, Part 1 and MK-4482-001 SARS-CoV-2 NGS analysis datasets described above for assessments of spike protein amino acid changes were used to characterize amino acid coding changes in the SARS-CoV-2 nsp12 (RdRp), and nsp14 (ExoN) genes. Again, results for all three MOV arms in each Phase 2 trial were pooled for analyses of treatment-emergent amino acid changes. Specific amino acid changes detected at the same amino acid position in \geq two participants (pooled MOV- and placebo-treated) were identified for each trial and tabulated.

Results of these analyses are summarized in [Table 32](#) and generally showed no clear patterns of MOV treatment-emergent amino acid substitutions in nsp12 or nsp14 in MK-4482-002, Part 1 or MK-4482-001. Consistent with the MOV mechanism of action, a greater proportion of participants in the MOV arms relative to the placebo arms had at least one treatment-emergent amino acid substitution or other change (e.g., deletion, insertion) detected in these targets, with the exception of nsp12 in MK-4482-001, and amino acid changes were scattered throughout the coding sequences.

There were no amino acid positions in nsp12 where treatment-emergent substitutions (or any other change) were detected at a \geq 5% frequency in \geq two participants in the pooled MOV/placebo population in MK-4482-002, Part 1. In MK-4482-001, only a single nsp12 substitution (G44V) was detected in \geq two participants, and it was enriched in the placebo group.

In both MK-4482-002, Part 1 and MK-4482-001, no emergent amino acid changes were detected in any participants at any of the following potential remdesivir resistance-associated positions in nsp12: F480, D484, V557, or E802.

In nsp14, A220S/V and V466I were each detected in two (2%) MOV-treated participants in MK-4482-002, Part 1. The impact of these changes is unknown. In a SARS-CoV-2 replicon system, nsp14 A220S or A220V site-directed substitutions did not reduce NHC antiviral activity. No nsp14 substitutions were detected at the same position in \geq two participants in MK-4482-001.

Table 32. Treatment-Emergent Amino Acid Changes (Through Day 5/EOT) Detected at ≥5% Frequency in nsp12 or nsp14, MK-4482-002, Part 1 and MK-4482-001

MK-4482-002, Part 1	# Participants in MOV Arms (Pooled, n=113)	# Participants in Placebo Arm (n=39)
nsp12 (RdRp)		
Any AA change	16 (14%)	2 (5%)
AA Positions with ≥2 participants with change		
None		
nsp14 (ExoN)		
Any AA change	16 (14%)	3 (8%)
AA Positions with ≥2 participants with change		
N129D	1	1
A220S/V	2 (1 S, 1 V)	0
V466I	2	

MK-4482-001	# Participants in MOV Arms (Pooled, n=89)	# Participants in Placebo Arm (n=27)
nsp12 (RdRp)		
Any AA change	9 (10%)	4 (15%)
AA positions with ≥2 participants with change		
G44V	1	2
nsp14 (ExoN)		
Any AA change	8 (9%)	0 (0%)
AA positions with ≥2 participants with change		
None		

Source: FDA analysis

Abbreviations: AA, amino acid, EOT, end of treatment; MOV, molnupiravir; nsp, nonstructural protein

Additional exploratory analyses were conducted to identify MOV treatment-associated amino acid changes in other viral nonstructural proteins (nsp1–11, nsp13, nsp15, or nsp16). In general, MOV treatment-emergent amino acid changes were scattered throughout these proteins, consistent with the random mutagenic effect of MOV, but there were no clear patterns of amino acid changes indicative of MOV resistance emergence.

Conclusion

In Phase 2 trials MK-4482-002, Part 1 and MK-4482-001, MOV treatment was not associated with any clear patterns of emergent amino acid changes in the nsp12 (RdRp) or nsp14 (ExoN) proteins that could indicate possible drug resistance. In addition, there was no evidence that MOV treatment enriched for SARS-CoV-2 variants with amino acid changes at nsp12 (RdRp) amino acid positions potentially associated with reduced SARS-CoV-2 susceptibility to remdesivir.

Therefore, the Division does not view MOV resistance or cross-resistance to remdesivir as significant risk issues at this time. Additional analyses of viral sequencing data from the larger MK-4482-002, Part 2 trial will be evaluated as they become available to continue to monitor these potential risks. Note that this topic was not discussed at the November 30, 2021, Advisory Committee meeting.

X. Specific Populations

- Safety and PK data are not available in pediatrics, pregnant or lactating women, patients with moderate or severe hepatic impairment, or patients with severe renal impairment. MOV is not authorized for use in pediatrics and not recommended in pregnant individuals. Breastfeeding is not recommended for 9 days (5 days of treatment with MOV and for 4 days after the final dose).
- No dose adjustment is recommended in geriatric patients and patients with any degree of renal or hepatic impairment.

XI. Human Clinical Pharmacology

1. Absorption, Distribution, Metabolism, and Excretion

- MOV is a prodrug, which is hydrolyzed by carboxylesterases (CES1 and CES2) to NHC either during or after absorption based on in vitro study results. Both MOV and NHC have high solubility and high intestinal permeability.
- A high-fat meal did not significantly impact the AUC (AUC_{last} and AUC_{0-inf}) of MOV or NHC, but it decreased the geometric mean of C_{max} of NHC by 36% and delayed median T_{max} by 2 hours. Decrease in the geometric mean C_{max} of NHC is not expected to be clinically relevant and thus MOV can be given with or without food.
- NHC is taken up by nucleoside uptake transporters into tissues, and intracellularly phosphorylated to the pharmacologically active triphosphate anabolite NHC-TP by host kinases, and then ultimately degraded to uridine and/or cytidine via the same pathways as those involved in endogenous pyrimidine metabolism.
- NHC is not bound to plasma proteins, whereas the plasma protein binding of MOV was not assessed.
- MOV is a weak substrate of human concentrative nucleoside transporter (CNT)1, not a substrate of CNT2, CNT3, equilibrative nucleoside transporter (ENT)1 or ENT2.
- NHC is a substrate of CNT1, CNT2, CNT3 and ENT2, and it could not be excluded as a substrate of ENT1 based on the 1.8-fold increase in NHC uptake in MDCKII-ENT1 cells. However, no apparent inhibition of this ENT-1 mediated transport was observed due to the parallel inhibition of endogenous uptake of NHC by S-(4-Nitrobenzyl)-6-thioinosine, a known inhibitor of ENT, in the control MDCKII cells.
- The percentage of MOV dose administered recovered in urine over the time interval of 0 to 12 hours was ~3% (coefficient of variation percent, 81.6%) following multiple oral doses of 800 mg Q12H MOV.
- The effective half-life of NHC is 3.3 hours.

2. Drug-Drug Interactions

No clinical drug-drug interaction studies have been conducted for MOV or NHC.

Potential drug-drug interaction liability of MOV or NHC as a victim (effect of other drugs on the absorption and disposition of MOV and NHC) is based on in vitro study results:

- MOV and NHC exhibits high solubility over gastrointestinal pH values and high intestinal permeability, thus gastric pH modifying agents are not expected to have a meaningful effect on MOV and NHC absorption.
- MOV and NHC are not substrates of CYP enzymes or human P-gp and breast cancer resistance protein transporters.
- MOV is a weak substrate of human concentrative nucleoside transporter 1 (CNT1), and is not a substrate of CNT2, CNT3, equilibrative nucleoside transporter1 (ENT1) or ENT2.
- The uptake of NHC into cells is mediated by host nucleoside transporters. NHC is a substrate of CNT1, CNT2, CNT3 and ENT2, and it could not be excluded as a substrate of ENT1. Based on the high transport capacity and functional redundancy of nucleoside transporters, coupled with the lack of clinically significant CNT or ENT mediated drug-drug interactions reported in the literature, clinically meaningful drug-drug interactions mediated by alteration of these transporters are not anticipated.
- The formation of NHC-TP from NHC is mediated by host kinases important in the regulation of endogenous pyrimidine nucleosides.

Potential drug-drug interaction liability of MOV or NHC as a perpetrator (effect of MOV or NHC on the absorption and disposition of other drugs) is based on in vitro study results. The mean $C_{max,ss}$ of MOV and NHC is 0.026 μ M and 8.99 μ M at the dose of 800 mg MOV every 12 hours, respectively.

- The potential for MOV and NHC to be reversible inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 was evaluated in the range of 0.13 to 100 μ M. At 100 μ M, neither MOV or NHC inhibited 50% of the marker activity of any CYPs tested, therefore, 50% inhibitory concentration (IC_{50}) values of MOV and NHC are greater than 100 μ M. At concentrations of 10 and 50 μ M, neither MOV nor NHC demonstrated time-dependent inhibition of any CYP enzyme (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4) evaluated.
- IC_{50} values of MOV and NHC are greater than 100 μ M (concentration range of MOV and NHC evaluated: 0.3 to 100 μ M) for OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, and MRP2 and greater than 1000 μ M (concentration range of MOV and NHC evaluated: 3 to 1000 μ M) for MDR1 (P-gp) and breast cancer resistance protein.
- Neither MOV nor NHC produced an induction response in CYP1A2, 2B6, and 3A4 mRNA or enzyme activity at concentrations up to 20 μ M (concentrations of MOV and NHC evaluated: 0.1 to 20 μ M).

Due to the concerns regarding the potential embryo-fetal toxicity, a reliable method of contraception is advised to individuals of childbearing potential for 9 days (5 days of treatment and for 4 days after the last dose of MOV), and thus the drug-drug interaction potential with hormonal contraceptives was considered. Overall, the potential in vivo drug-drug interaction liability of MOV or NHC as a victim or perpetrator appears to be low and it is unlikely that MOV

or NHC will have a clinically significant pharmacokinetic drug-drug interaction with co-administered drugs, including hormonal contraceptives. The drug-drug interaction between MOV/NHC and concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

3. Pharmacokinetics

The method validation and study sample analyses used to measure MOV and/or its metabolites in plasma, urine, and PBMC were found to be acceptable. All samples were analyzed within established analyte stability duration.

The prodrug MOV is rapidly metabolized to NHC, resulting in little to no systemic exposure of MOV. The pharmacokinetics of plasma NHC in healthy participants and patients with COVID-19 and the pharmacokinetics of NHC-TP in PBMCs in healthy participants after multiple oral doses of MOV are shown in [Table 33](#) and [Table 34](#), respectively. Pharmacokinetics of NHC has not been evaluated in specific populations including pediatrics, several renal impairment, moderate and severe hepatic impairment, pregnant women, and lactating women. Population PK analysis results indicated that [age (in adults ≥ 18), body weight, BMI, sex, race, ethnicity, mild hepatic impairment, mild-to-moderate renal impairment, disease severity] did not have a clinically significant effect on NHC exposures (refer to [Figure 10](#) in Section XXVII.8).

Table 33. Pharmacokinetic Parameters of Plasma NHC After Multiple Oral Doses of 800 mg MOV Every 12 Hours

Parameter	Healthy Participants Geometric Mean (CV%)	Patients With COVID-19 Geometric Mean (CV%)
N	6	449 (178 for C_{max})
C_{max} (ng/mL)	2970 (16.8)	2330 (36.9)
AUC _{0-12h} (ng/mL*hr)	8330 (17.9)	8260 (41)
C_{12h} (ng/mL)	16.7 (42.8)	31.1 (124)

Source: Reviewer's table based on study report MK-4482-004 for healthy participants and population pharmacokinetic memo for patients with COVID-19 patients

Abbreviations: AUC, area under the curve; C_{max} , maximum plasma concentration; COVID-19, coronavirus disease 2019; CV, coefficient of variation; MOV, molnupiravir; N, number of participants; NHC, N3-hydroxycytidine

Table 34. Pharmacokinetic Parameters of NHC-TP in PBMCs After Multiple Oral Doses of 800 mg MOV Every 12 Hours in Healthy Participants

Parameter	Geometric Mean (CV%)
N	6
C_{max} (nM)	28600 (48.6)
AUC _{0-12h} (nM*hr)	275000 (46.5)
C_{12h} (nM)	16200 (42.7)

Source: Reviewer's table based on preliminary PK data from study P012.

Abbreviations: AUC, area under the curve; C_{max} , maximum plasma concentration; CV, coefficient of variation; MOV, molnupiravir; N, number of participants; NHC-TP, N3-hydroxycytidine triphosphate; PBMCs, peripheral blood mononuclear cells

XII. Additional Nonclinical Data to Support Safety

Nonclinical reproductive toxicology, bone/cartilage toxicity, and genetic toxicology findings are discussed in Section IX.4 above. Other nonclinical safety data that do not rise to the level of risk mitigation were:

1. Central Nervous System

- No effects were noted for the central nervous system or body temperature in vivo in rats up to 16 times the human exposure (C_{max}).

2. Cardiovascular System

- Low risk of QT prolongation in vitro
- There were no effects on electrocardiogram or cardiovascular endpoints up to 5 times the clinical exposure in vivo in dogs.

3. Respiratory System

- No effects noted in rats up to 16 times the human exposure (C_{max}).

4. PK/ADME/TK

- Oral bioavailability was 37–45% in mice. Dose proportional exposure was noted with NHC and NHC-triphosphate in the brain, spleen, lung, and heart. The spleen and lung (in that order) had the most exposure to both NHC and NHC-triphosphate.
- In dogs and ferrets, tissue concentrations of NHC-TP tended to be greater than tissue concentrations of NHC. Conversely, in rats and monkeys, tissue concentrations of NHC tended to be greater than tissue concentrations of NHC-TP.

5. 7-Day Toxicology Findings

- Mild hematology decreases and slight AST/ALT increases in rats at 7 days.
- High dose toxicity in dogs associated with shock and tachycardia as well as decreases in testicular and epididymis weights (males) and ovaries and uterine weights (females) at 7 days in dogs.

6. 28-Day Toxicology Findings

- There were no toxicologically significant findings in rats at NHC exposures up to 4 to 8 times the human exposure.
- In dogs, significant findings included the following:
 - Severe thrombocytopenia, 10-fold decrease in platelet counts, with subsequent hemorrhage in multiple tissues, especially in the GI track, but also in brain, spinal cord, gall bladder, thymus and mediastinal tissue and urinary bladder
 - Severe/marked bone marrow cellularity decreases at 17 and 50 mg/kg in femur and sternum
 - 10-fold increase (males) and 250-fold increase (females, with no observable erythroid precursors) in bone marrow M:E ratio at 50 mg/kg
 - Platelet values in treated dogs tended to match control animals during the recovery period
 - Systemic exposures to NHC at the NOAEL were 0.1-fold the clinical NHC AUC at 800 mg Q12H

7. 3-Month Toxicology Findings

- Bone and cartilage effects were noted (discussed in Section [IX.4](#) above).
- Other findings included the following:
 - Decreased mean body weight gain and food consumption at exposures approximately equivalent to the mean clinical NHC exposure at 800 mg Q12H
 - Seminiferous tubule degeneration in 2 of 10 males and depletion of secretory acidophil cells of the pituitary in 9 of 10 males at exposures 15-fold the mean clinical NHC exposure at 800 mg Q12H.

8. Ongoing Studies

A study in juvenile rats to assess the potential impact of MOV on bone and cartilage development is ongoing. Until that study is complete and has been reviewed by the Agency, MOV is not advised for use in pediatric patients.

A carcinogenicity study in a transgenic mouse model is ongoing and will be reviewed upon submission.

A pharmacokinetic/distribution study in rats, specifically to determine distribution of NHC to testes, is ongoing. If NHC is detected in testes, the Sponsor will complete an assessment of mutant frequencies in testicular germ cells from transgenic Big Blue[®] rats.

SEE ATTACHED ADDENDUM

XIII. Nonclinical Data to Support Efficacy

1. Mechanism of Action

MOV is a 5'-isobutyrate prodrug of a mutagenic cytidine ribonucleoside analogue, β -D-N⁴-hydroxycytidine (NHC, EIDD-1931). 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 RdRp, nsp12, and the NHC-monophosphate (NHC-MP) is incorporated into 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 (Flavell et al. 1974).

Over time, as NHC-MP is incorporated into viral RNA genomes and copied, changes accumulate in the viral genome, particularly G \leftrightarrow A and C \leftrightarrow 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.

2. Summary of Data Reviewed for Nonclinical Virology-Related Studies

Mechanism of Action and Cell Culture Antiviral Activity Studies

- In biochemical assays, NHC-TP could be used as a substrate by recombinant SARS-CoV-2 RdRp for incorporation into RNA. NHC competes primarily with C for incorporation into RNA, but it can also compete with U and thus can incorporate into RNA opposite of G or A in the RNA template leading to transition mutations (Gordon et al. 2021; Kabinger et al. 2021).
- NHC-TP is weakly competitive with natural ribonucleotides for use as a substrate by the SARS-CoV-2 RdRp. According to Gordon et al., 2021, SARS-CoV-2 RdRp shows a 30-fold preference for cytidine triphosphate over NHC-TP. Selectivity of the SARS-CoV-2 RdRp for other host ribonucleotides over NHC-TP was even greater at 171-, 424- and 12,841-fold for uridine triphosphate, adenosine triphosphate and guanosine triphosphate, respectively.
- The incorporation of NHC-MP does not cause RNA chain termination like other conventional antiviral nucleoside analogues. Rather, the RNA chain can continue to elongate, and subsequently, the incorporated NHC-MP can be used as a template by the viral RdRp for incorporation of G or A, further increasing the numbers of transition mutations (Gordon et al. 2021; Kabinger et al. 2021).
- In cell-based assays, NHC inhibited the replication of multiple different coronaviruses (including human coronaviruses and mouse hepatitis virus [MHV]), which was associated with increases in nucleotide changes, primarily transition mutations, throughout the viral genomes (Agostini et al. 2019; Sheahan et al. 2020).

- MOV antiviral activity in a Middle East respiratory syndrome coronavirus (MERS-CoV) mouse model was associated with increased numbers of transition mutations in viral genomes (Sheahan et al. 2020).
- NHC had cell culture antiviral activity against SARS-CoV-2 across multiple independent experiments and in a variety of cell types, with 50% effective concentration (EC_{50}) values at sub- to low micromolar concentrations (range: 0.32 to 2.66 μ M in A549 and Vero E6 cells), and selectivity indices generally >10.
- NHC had consistent cell culture antiviral activity against SARS-CoV-2 isolates representing different variants of concern/interest, including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta).
- NHC had nonantagonistic antiviral activity with remdesivir against SARS-CoV-2 in a cell culture assay.
- NHC had no or minimal binding with mouse, rat, dog, cynomolgus monkey or human plasma proteins, as measured by equilibrium dialysis.

Assessments of Cytotoxicity and Off-Target Activity

- NHC had a wide range of 50% cytotoxicity (CC_{50}) values across a variety of different human and animal cell types. The most sensitive cell line evaluated was human lymphoid CEM cells, for which NHC had a CC_{50} value of 7.5 μ M (Sticher et al. 2020).
- MOV inhibited the proliferation of human bone marrow progenitor cells with CC_{50} values of 24.9 μ M and 7.7 μ M for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays. The cytotoxicity of NHC in this assay was not determined, but it is assumed that NHC would have similar CC_{50} values in this assay based on NHC generally having comparable or lower CC_{50} and EC_{50} values than MOV across a variety of cell culture assays.
- NHC-TP is a weak substrate for human mitochondrial RNA polymerase resulting in incorporation of NHC-MP into mitochondrial RNA. The efficiency of NHC-TP as a substrate for mitochondrial RNA polymerase was estimated to be approximately 740-fold lower compared to natural cytidine triphosphate. Cell-based assays indicate NHC generally does not have highly specific effects on mitochondrial function (Sticher et al. 2020).
- There are multiple published reports that NHC-TP can act as a substrate for other RNA polymerases, including the human nuclear DNA-dependent RNA polymerase II enzyme that is responsible for mRNA synthesis. However, NHC-TP appears to have some selectivity for viral RNA polymerases over host RNA polymerases, and incorporation of NHC-MP by host RNA polymerases appears to be relatively inefficient compared to natural nucleotides (Stuyver et al. 2006; Suzuki et al. 2006; Toots et al. 2019). Incorporation of NHC-MP was not observed in cellular RNAs in ferret and mouse studies of MOV based on analyses of transition mutation rates in polymerase chain reaction-amplified complementary DNA (Toots et al. 2019; Sheahan et al. 2020).
- In biochemical assays, NHC-TP did not inhibit the human DNA polymerases α , β , or γ , with IC_{50} values >1,000 μ M (Sticher et al. 2020).

Resistance Development in Cell Culture and Cross-Resistance

- MOV (primarily from studies with NHC) appears to have a relatively high resistance barrier, and to date, there are no known amino acid changes in SARS-CoV-2 that confer resistance to MOV or NHC.
- The full potential for cross-resistance between MOV/NHC and remdesivir remains unknown and should continue to be monitored and characterized in clinical and nonclinical studies, although based on currently available data there is no clear evidence of a cross-resistance signal between MOV/NHC and remdesivir. The active metabolites of both MOV/NHC and remdesivir interact with the viral RdRp complex and are incorporated into elongating viral RNA genomes, but their precise mechanisms of action differ in that remdesivir causes RNA chain termination, while NHC incorporation does not cause chain termination but leads the accumulation of mutations in viral genomes.
- Resistance to NHC was not readily selected by repeated passage of MHV or MERS-CoV in cell culture in the presence of NHC (Agostini et al. 2019). In this study MHV and MERS-CoV were passaged 30 times in the presence of increasing concentrations of NHC (up to 5 μ M for MHV, up to 6.5 μ M for MERS-CoV) in two independent passages for each virus. The passaged viruses had modest changes in susceptibility to NHC, with approximately 2-fold increases in EC₉₀ values. Consistent with the mutagenic activity of NHC, the passaged viruses had numerous synonymous and nonsynonymous nucleotide mutations scattered throughout their genomes (27 to 162 total nucleotide changes after 30 passages).
- For NHC-passaged each virus, there was one position in nsp12 where amino acid substitutions emerged in both independent NHC passages: A234T/V in MHV and V558I in MERS-CoV, corresponding to positions V234 and V557 in SARS-CoV-2, respectively. The nsp12 V558I substitution that emerged in NHC-selected MERS-CoV is notable as this corresponds to the same amino acid position where a remdesivir resistance-associated substitution was identified in MHV (V553L) and SARS-CoV-1 (V557L) (Agostini et al. 2018). However, analysis of SARS-CoV-2 sequence data from clinical trials did not identify MOV treatment-emergent substitutions at this position.
- None of the following reported remdesivir resistance-associated substitutions in nsp12 conferred reduced phenotypic susceptibility to NHC in a SARS-CoV-2 replicon system: F480L (Agostini et al. 2018), D484Y (Martinot et al. 2021), V557L (Martinot et al. 2021), E802A (Szemiel et al. 2021), and E802D (Agostini et al. 2018). In all cases NHC EC₅₀ values for the site-directed mutant replicons were <1.6-fold relative to a wild-type replicon. These substitutions reduced remdesivir activity in the same assay by 1.6- to 2.5-fold.
- The SARS-CoV-2 replicon system was also used to assess the impact of the following substitutions in nsp12 and nsp14, which were detected as possible MOV treatment-emergent substitutions in the Sponsor's Phase 2 resistance analyses: NSP12_T739I, NSP14_A220S, NSP14_A220T, NSP14_A220V, NSP14_S503L, and NSP14_S503P. NHC EC₅₀ values for replicons with these substitutions were all <1.6-fold relative to a wild-type replicon.

Activity in Animal Models of SARS-CoV-2 Infection

MOV was shown to have antiviral activity in multiple animal models of SARS-CoV-2 infection, particularly when first administered prior to, or soon after viral challenge. Key published studies are summarized briefly as follows:

- MOV had anti-SARS-CoV-2 activity in a humanized mouse model in which immune deficient mice are implanted subcutaneously in the back with human lung tissue, referred to as human “lung-only mice” (Wahl et al. 2021). Mice were orally administered a relatively high dose of MOV (500 mg/kg) or vehicle control, 12 hours prior, 24 hours post- or 48 hours post-inoculation of the human lung tissue with SARS-CoV-2 (USA-WA1/2020), followed by twice daily (BID) dosing thereafter. Lung tissue was harvested 48 hours following virus inoculation or initiation of treatment. All three MOV dosing strategies were associated with reduced levels of virus detected in the lung tissues.
- MOV anti-SARS-CoV-2 activity was demonstrated in a nonlethal ferret model of infection (Cox et al. 2020). In one experiment, ferrets were challenged intranasally with 10⁵ plaque-forming unit SARS-CoV-2 (2019-nCoV/USA-WA1/2020) and then administered MOV at 5 or 15 mg/kg BID starting 12 or 36 hours postchallenge. MOV dosing was associated with reduced SARS-CoV-2 viral titers in nasal washes within 12 hours of initiating dosing, and also in nasal turbinate tissues collected on Day 4 postchallenge. In a second experiment, infected ferrets were treated with MOV or vehicle and cohoused with uninfected and untreated contact ferrets. The contact ferrets of vehicle-treated infected animals began to shed SARS-CoV-2 within 20 hours of cohousing, while no virus (plaque-forming unit or RNA) was detected in the ferrets that were in contact with MOV-treated ferrets, indicating MOV inhibited SARS-CoV-2 transmission in this model.
- MOV (250 mg/kg) was active in a nonlethal Syrian hamster model of SARS-CoV-2 infection when administered starting at 12 hours prior to or 12 hours following viral challenge (Rosenke et al. 2021). Another independent study using the Syrian hamster model showed MOV (200 mg/kg) had consistent antiviral activity against SARS-CoV-2 B.1-G (Wuhan isolate), B.1.1.7 (Alpha), or B.1.351 (Beta) variants (Abdelnabi et al. 2021).

Substantially different doses of MOV were used to demonstrate antiviral activity in different animal species, which can be attributed to differences in efficiency of NHC-TP production in tissues. For example, in ferrets, oral doses as low as 5 mg/kg BID were associated with anti-SARS-CoV-2 activity (Cox et al. 2020). NHC is also active against influenza virus with EC₅₀ values similar to those against coronaviruses, and it was shown that similarly low doses of MOV had activity against influenza virus in ferrets (Toots et al. 2019).

On the other hand, much higher doses of MOV (≥400 mg/kg BID) were needed for optimal anti-SARS-CoV-1) and anti-influenza virus activity in mice (Yoon et al. 2018; Sheahan et al. 2020). Following a single oral dose of MOV, comparable lung NHC-TP levels were detected in mice that received MOV at a 635 mg/kg dose and ferrets that received MOV at a 20 mg/kg dose. Furthermore, the plasma C_{max} levels of NHC associated with these lung NHC-TP concentrations were 12-fold higher in mice compared to ferrets. During the review this observation raised questions about whether tissue NHC-TP concentrations reach clinically relevant levels in rodent mutagenicity studies, but further analyses of NHC-TP concentrations in different animal species indicate clinically relevant concentrations of NHC-TP are likely achieved at the MOV doses evaluated in nonclinical rodent studies (see also Section [IX.4.1](#) on mutagenicity risk).

XIV. Supply Information

Quantity of drug product needed for one treatment course per individual for proposed emergency authorized use (adults, pediatrics): 40 capsules are required for each treatment course.

SEE ATTACHED ADDENDUM

The Sponsor stated in an email dated December 13, 2021, that they have completed manufacturing of the 3.1 million patient treatment courses currently allocated to the U.S. market based on the agreed terms of the Biomedical Advanced Research and Development Authority contract. Packaging of capsules has initiated with (b) (4) patient treatment courses already packaged and located in their distribution center. The Sponsor stated that they plan to continue packaging in order to have the entire 3.1 million patient treatment courses available for release by the end of January 2022.

XV. Chemistry, Manufacturing, and Controls Information

The active ingredient, MOV, is manufactured (b) (4). MOV is an ester prodrug of N3-hydroxycytidine (NHC). Its structure was adequately characterized, and its manufacturing was sufficiently described and was found reasonable to produce consistent drug substance. (b) (4) is an adequately justified starting material and complies with the principles of ICH Q11. (b) (4)

(b) (4) Drug substance in-process controls during development and EUA drug substance specifications were determined to be suitable to assure the quality of the drug substance.

Two specified impurities ((b) (4)) with limits above the ICH Q3A qualification threshold were confirmed to be acceptable by the nonclinical reviewer for this EUA. The risk for elemental impurities, nitrosamines, and residual solvents were adequately addressed by controls at the starting material and API manufacturing sites and by confirmatory testing by the Office of Pharmaceutical Quality's Office of Testing and Research. Data supported a 24-month drug substance retest period.

The Sponsor proposes to use drug substance from four manufacturers for inclusion in this application (b) (4). There are two drug substance intermediate suppliers which supply these sites: (b) (4). Further, drug substance from three development manufacturers were also used to manufacture EUA drug product: (b) (4).

Batch data from all sites were found to be comparable with respect to quality and all met the proposed specification. API from all seven drug substance manufacturers will be used in drug product for the initial EUA distribution. The three developmental drug substance suppliers are being phased out for production, while some newer commercial suppliers such as (b) (4) have provided release data for only a few batches. Although the manufacturing process slightly differs during development (i.e., process 1A, 1B, 1C, 1D, and 1E reported), all processes (b) (4)

(b) (4) The chemistry, manufacturing, and controls information submitted demonstrates an appropriate risk-based approach to controlling drug substance quality for an initial EUA.

The drug product are 200 mg strength capsules packaged in 40-count high-density polyethylene bottles with a polypropylene induction sealed closure. (b) (4) % w/w of the capsule fill is drug substance with (b) (4) % microcrystalline cellulose ((b) (4)), (b) (4) % hydroxypropyl cellulose ((b) (4)), (b) (4) % croscarmellose sodium ((b) (4)) and (b) (4) % magnesium stearate ((b) (4)). All inactive (b) (4) ingredients including the capsule and inks are Compendial.

The Sponsor initially proposed to distribute 34 million capsules without an imprint, which was 25% of the Sponsor’s planned U.S. government supply. After discussions with the Office of New Drugs, the Sponsor was informed on November 16, 2021, by the Agency that, “The public health benefits of having all solid oral dosage forms contain imprinting include, among other things, the ability to easily and uniquely identify the drug product dispensed, in this case for self-administration, and to reduce the potential for medication errors. Given the importance of imprinting, FDA intends to authorize only those finished capsules of MOV that contain imprinting at this time.”

Each 200 mg strength capsule has a total fill weight target of (b) (4) mg. The manufacturing process includes (b) (4)

(b) (4). The process was developed from lab scale, scale up to pilot scale, then to commercial scale. The process parameter ranges and proposed IPCs and their limits are adequately justified. The drug product is manufactured at three sites: (b) (4), (b) (4), and (b) (4). The manufacturing process used at each site was comparable, as was the quality of product from each of the sites.

The Sponsor was informed on November 16, 2021, that their data supported a 24-month expiry period.

XVI. Manufacturing Site Inspections

All of the manufacturing sites evaluated listed below are associated with IND 147734, and the commercial Sponsor is Merck Sharp & Dohme., a subsidiary of Merck & Co., Inc.

Table 35. Manufacturing Site Inspections

Manufacturing Site Identifier (b) (4)	Drug Substances / Intermediates/ Drug Product / Testing / Labeler / Packager	Location (U.S. and Non-U.S.) (b) (4)	Inspection Dates (b) (4)	GMP Status (if Known)
(b) (4)	DS and DS intermediate manufacturing and testing	(b) (4)	(b) (4)	Acceptable
(b) (4)	DS and DS intermediate manufacturing for initial EUA batches only	(b) (4)	(b) (4)	Acceptable
(b) (4)	DS manufacturing and testing for initial EUA batches only	(b) (4)	(b) (4)	Acceptable
(b) (4)	DS and DS intermediate manufacturing and testing for initial EUA batches only	(b) (4)	(b) (4)	Acceptable
(b) (4)	DS and DS intermediate manufacturing and testing	(b) (4)	(b) (4)	Acceptable
(b) (4)	DS and DS intermediate manufacturing and testing	(b) (4)	(b) (4)	Acceptable ¹
(b) (4)	DS and DS intermediate manufacturing and testing	(b) (4)	(b) (4)	Acceptable

(b) (4)	DS Intermediate manufacturing	(b) (4)	Acceptable
	DS Intermediate manufacturing testing for DS		Acceptable
	DS Intermediate manufacturing		Acceptable
	DP manufacturing and testing		Acceptable
(b) (4)	DP manufacturing and testing	(b) (4)	Acceptable
(U) (4)	DP manufacturing packaging, and testing	(b) (4)	Acceptable
	Testing for DS		Acceptable
	Testing for DS		Acceptable
	Testing for DS		Acceptable
(b) (4)	Testing for DP	(b) (4)	Acceptable
(b) (4)	Microbial Testing for DP	(b) (4)	Acceptable
(b) (4)	Labeler / Packager	(b) (4)	Acceptable
(b) (4)	Labeler / Packager	(b) (4)	Acceptable
	Testing for DS		Acceptable
	Starting material manufacturing		OAI ²
	Starting material manufacturing		OAI ³

¹ (b) (4) was inspected by the FDA from (b) (4). No issues were identified, and the inspection was classified NAI.

² (b) (4) was inspected by FDA from (b) (4) and determined that the inspection classification of this facility is OAI, and the facility will remain on Import Alert 66-40. To mitigate the risk, the Sponsor has committed to performing additional screening for foreign contamination (e.g., (b) (4)) on all lots of (b) (4) used in the manufacture of MOV API.

³ (b) (4) was last inspected by the FDA from (b) (4) and determined that the inspection classification of this facility is OAI. To mitigate the risk, the Sponsor has committed to performing additional (b) (4) testing for all lots of (b) (4) used in the manufacture of MOV API until further notification by FDA.

Abbreviations: DP, drug product; DS, drug substance; EUA, Emergency Use Authorization; GMP, good manufacturing practice; OAI, official action indicated; U.S., United States

Based on FDA's evaluation of the manufacturing process and control strategy, and the listed facilities, FDA considers the following conditions to the authorization as necessary to protect the public health⁸:

- The Sponsor will manufacture MOV to meet all quality standards and per the manufacturing process and control strategy as detailed in the Sponsor's EUA request. The Sponsor will also test the API starting material for additional quality attributes agreed upon by the Sponsor and the Agency. The Sponsor will not implement any changes to the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy that assure process performance and quality of the authorized product, without notification to and concurrence by the Agency as described under condition D.
- All manufacturing, packaging, and testing sites for both drug substance and drug product will comply with current good manufacturing practice requirements of the Federal Food, Drug, and Cosmetic Act, Section 501(a)(2)(B).
- The Sponsor will submit information to the Agency within three working days of receipt concerning significant quality problems with distributed drug product of MOV that includes the following:
 - Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another articleOR
 - Information concerning any microbiological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet established specifications

If a significant quality problem affects unreleased product and may also impact product(s) previously released and distributed, then information must be submitted for all potentially impacted lots.

The Sponsor will include in its notification to the Agency whether the batch, or batches, in question will be recalled. If FDA requests that these, or any other batches, at any time, be recalled, the Sponsor must recall them.

If not included in its initial notification, the Sponsor must submit information confirming that the Sponsor has identified the root cause of the significant quality problems, taken corrective action, and provide a justification confirming that the corrective action is appropriate and effective. The Sponsor must submit this information as soon as possible but no later than 45 calendar days from the initial notification.

- The Sponsor will list MOV with a unique product National Drug Code under the marketing category of Emergency Use Authorization. Further, the listing will include each establishment where manufacturing is performed for the drug and the type of operation performed at each such establishment.

⁸ See the evaluation documented in OMQ's Authorization Recommendation Memo for Emergency Use Authorization in CMS Case #621564, J, as well as OPQ's Chemistry, Manufacturing, and Controls EUA Assessment Memo, dated December 21, 2021, associated with EUA 108.

XVII. Clinical Trial Site Inspections

Clinical trial site inspections were not conducted for this EUA. Office of Scientific Investigations (OSI) requested the following information to determine if a good clinical practice inspection was warranted. Based on review of the submitted data and documents, OSI did not observe any signals that would trigger a good clinical practice inspection during the review of the EUA.

OSI's information request (IR) on November 11, 2021, for Part 2 of MK-4482-002 included requests for site-specific information such as number of participants screened, enrolled, randomized, and discontinued; efficacy and safety data by country and site; and the Sponsor's quality assurance plan, including their monitoring plan and data management plan.

OSI reviewed the Sponsor's November 19, 2021, response to the IR. The Sponsor's site monitoring plan and data management plan appeared adequate. The line listings provided by the Sponsor were not enough to determine if there were any outliers in the efficacy result or reported AEs and SAEs by country and by site for Part 2 of MK-4482-002. The majority of the data from this study were obtained outside the United States.

A follow-up IR was sent in order to obtain additional information to determine if there were any outliers with respect to efficacy or safety. OSI reviewed the Sponsor's December 6, 2021, response regarding the incidence of hospitalization or death through Day 29 by country and site in the mITT population; and AEs and SAEs by country and site during treatment and the 14-day follow-up period in all study participants. It appears that Brazil and Guatemala were outliers for incidence of hospitalization or death through Day 29. However, in Guatemala, the results favored placebo. There did not appear to be any outliers for AEs. In terms of SAEs, at least one SAE was reported in the majority of countries. The three countries without a participant with a reported SAE randomized a small number of participants (Argentina n=1; France n=7; and Germany n=2).

XVIII. Animal Study Site Inspections (Efficacy and PK/PD)

Nonclinical site inspections were not conducted for this EUA.

XIX. Recommendations From Treatment Guidelines and Other Sources

At the time of this review, the COVID-19 Treatment Guidelines Panel recommends using either bamlanivimab plus etesevimab, or casirivimab plus imdevimab or sotrovimab to treat outpatients with mild-to-moderate COVID-19 who are at high risk of clinical progression. The strength of the evidence for using anti-SARS-CoV-2 mAbs varies depending on the medical conditions and other factors that place patients at high risk for progression to severe COVID-19 and/or hospitalization. See the National Institutes of Health (NIH) COVID-19 Treatment Guidelines (NIH 2021) for further details.

The Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients With COVID-19 (IDSA 2021) states: Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the Infectious Diseases Society of

America guideline panel suggests bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab rather than no neutralizing antibody treatment. (Conditional recommendation, Moderate certainty of evidence)

XX. Advisory Committee Summary

Below is a summary of the Advisory Committee discussion (FDA 2021)⁹.

Questions to the Committee

Discussion 1: Potential Use of MOV During Pregnancy, Both in Terms of Risk and Benefit

1. Comment if you think MOV should be accessible for use in pregnancy in certain scenarios, and if so, please describe what those scenarios might be.
2. Do the concerns regarding the use of MOV during pregnancy extend to the use of MOV in individuals of childbearing potential? If so, are there mitigation strategies that should be considered?

Committee Discussion

Committee members described the following as possible scenarios in which MOV should be made accessible to pregnant individuals: those with multiple comorbidities who are early in their disease course and are not being effectively treated with monoclonal antibodies (mAbs), or for whom alternative treatments are not available or accessible. Committee members also considered the pregnancy trimester a possible factor in deciding to use MOV. There appeared to be consensus that MOV should not be used in the first trimester.

In general, Committee members agreed that the decision to use MOV should be made using a shared decision-making approach to ensure that pregnant individuals are informed of MOV's potential fetal risks. One Committee member stated that there would not be a scenario in which they would recommend MOV to a pregnant individual.

With regards to use of MOV in individuals of childbearing potential, the Committee members agreed with the Agency's proposed mitigation strategies to confirm that a woman is not pregnant and is using effective contraception before taking MOV. Several Committee members noted that a shared decision-making approach should still be used in these individuals. Please see the transcript for details of the Committee's discussion.

Discussion 2: Concern Regarding Observed Increased Rate of Viral Mutations Involving Spike Protein Among Participants Receiving MOV

1. Comment on what, if any, additional risk mitigation strategies or limitations on the authorized population could be considered.

⁹ See the following website for the Advisory Committee meeting information and event materials: <https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-30-2021-antimicrobial-drugs-advisory-committee-meeting-announcement-11302021-11302021>

2. What monitoring strategies should be considered to better understand and mitigate these concerns?

Committee Discussion

Overall, most Committee members expressed concerns over the mutagenicity of MOV on the viral genome, particularly in the spike gene. Committee members agreed that there should be risk mitigation strategies for individuals receiving MOV to prevent escape of potentially novel viral variants. One Committee member recommended the continued use of precautions such as avoiding sharing rooms with individuals on treatment, wearing masks, and completing two negative SARS-CoV-2 tests prior to ending isolation.

Another Committee member suggested using pharmacies to facilitate viral sampling of individuals receiving MOV as a monitoring strategy to better understand the risk of generating and spreading viral variants. However, one Committee member noted that the overall impact of MOV on viral evolution may be minimal given that selective pressures on the spike protein, which are not directly affected by the drug, are the primary driver of SARS-CoV-2 evolution.

Although some other Committee members similarly noted their concerns over the increased rate of viral mutations are lessened given the drug's ability to quickly reduce virus production, there were specific concerns over prolonged viral replication in immunocompromised individuals. These Committee members expressed a need for additional studies in immunocompromised individuals. Please see the transcript for details of the Committee's discussion.

Vote

1. Do the known and potential benefits of MOV outweigh the known and potential risks of MOV when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death?
 - a. If yes, please describe the appropriate authorized population such as risk factors for disease progression and pregnant individuals. Please comment on the proposed risk mitigation strategies and if additional risk mitigation strategies are needed.
 - b. If no, please describe your reasons for concluding that the overall benefit-risk for MOV is not favorable for any population based on the data available at this time.

Vote Result

Yes: 13 No: 10 Abstain: 0

Committee Discussion

A slight majority of Committee members voted that the known and potential benefits of MOV outweighed its known and potential risks when used for the treatment of mild-moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death.

Committee members who voted "Yes" described the authorized population as high-risk, unvaccinated individuals. Some Committee members stated they would not recommend MOV in pregnant individuals unless alternative treatments were not available. These Committee members also recommended against its use during the first trimester of pregnancy. Several Committee members who voted "Yes" expressed concern about potential mutagenicity. In general, Committee members were supportive of the Agency's proposed risk mitigation

strategies and mentioned additional strategies such as shared decision-making prior to treatment and minimizing household contacts while on treatment.

Committee members who voted “No” cited the following as reasons for concluding that the overall benefit-risk ratio was unfavorable: (1) a high number-needed-to-treat compared with placebo, (2) unclear efficacy against the Delta variant, (3) potential to drive viral mutations, and (4) mutagenicity risks. Several Committee members also expressed concerns over monitoring treatment adherence. Overall, Committee members agreed there is a need for additional safety data, as well as further studies in the vaccinated and immunocompromised. Please see the transcript for details of the Committee’s discussion.

XXI. Benefit-Risk Assessment and Recommendations for Emergency Use

In a single Phase 3 trial in 1433 high-risk adults with mild-to-moderate COVID-19, a 5-day course of the oral antiviral MOV was associated with an adjusted risk difference of -3% and an adjusted relative risk reduction of 30% in hospitalization or death through Day 29 compared to placebo. Notably, at an interim analysis of data from 50% of the planned population (N=775), MOV was associated with a 48% relative reduction, which led to the trial being stopped early for efficacy. The cause of the decrease in efficacy between the first and second half of the trial remains unclear. At the time of this review, no therapies are FDA-approved for the treatment of mild-to-moderate COVID-19, though three mAb regimens requiring IV or SC administration are authorized under EUA for this use.

MOV was generally safe and well tolerated among clinical trial participants. However, several potential risks to patients have been identified based on findings from the available nonclinical data and include the risk of embryo-fetal toxicity, impaired bone and cartilage growth, and mutagenicity. Additional nonclinical data are being collected to better understand the risks these findings pose to patients, including a juvenile toxicology study, carcinogenicity study, and a germ cell study. Lastly, in addition to the known and potential risks to individual patients, there is also a potential risk based on the finding of an increased rate of amino acid changes in the SARS-CoV-2 spike protein among participants treated with MOV. The clinical and public health implications of this finding remain uncertain. Fortunately, these changes did not appear to be associated with hospitalization or death among the small subset of participants from MOV clinical trials for whom these data are available. However, on a large scale, these changes could, in theory, enhance SARS-CoV-2 spike protein evolution. It is not clear that further restrictions on the authorized population would be sufficient to meaningfully impact this trajectory should these theoretical concerns be realized.

Given that the potential risks of MOV are offset by only modest clinical benefit and given that there are other authorized products for the same use that have more favorable benefit-risk profiles, the review team has concluded that MOV should be authorized as a second line agent. Specifically, we recommend that MOV be authorized for the 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. The authorization will be limited to patients who are within 5 days of symptom onset.

Within the framework of second-line usage, high-risk for progression to severe disease will be defined in accordance with the CDC’s high-risk criteria. Data on efficacy in various high-risk

subgroups represented in MK-4482-002 will be reported in the fact sheet to inform the benefit/risk assessment of MOV use in individual patients. Similarly, prescribers should factor a patient's COVID-19 vaccination status into the benefit/risk assessment. Irrespective of COVID-19 vaccination status, MOV may provide benefit in high risk patients with mild-to-moderate COVID-19 for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Given the embryo-fetal toxicity and bone and cartilage findings, the use of MOV during pregnancy is generally not recommended. However, the review team, taking into consideration the data and the advice of the Advisory Committee members, has concluded that there may be certain clinical situations in which the known and potential benefits of MOV outweigh the potential risks of MOV use during pregnancy. There will be a Warning and Precaution in the health care provider fact sheet describing the potential for fetal harm should MOV be used during pregnancy. The prescribing health care provider will be required to document that the patient has been informed about the benefits and risks of taking MOV during pregnancy. Further, the Agency has proposed recommendations for contraception use and assessing pregnancy status. Lastly, the Sponsor will collect data on pregnancy exposures and outcomes via a pregnancy surveillance program.

Given potential impact of MOV on bone and cartilage growth, the generally benign COVID-19 disease course in pediatric patients, and the availability of other therapies authorized for use in pediatric patients, there are no situations in which the known and potential benefits of MOV are thought to outweigh the known and potential risks in pediatric patients. Therefore, MOV will not be authorized for use in pediatric patients and the health care provider fact sheet will include a Warning and Precaution describing the potential risks to pediatric patients.

Lastly, the overall risk of mutagenicity in humans is considered low. The risk of mutagenicity in association with MOV use under the EUA will be further reduced by the short, 5-day treatment course and statements on the Fact Sheets stipulating that MOV not be authorized for use for more than 5 consecutive days and that MOV be dispensed in the original container as a single treatment course. In addition, until data regarding the potential for MOV to induce germ cell mutations, male patients will be advised to use effective contraception for 90 days after the last dose of MOV. The risk beyond 3 months after the last dose of MOV is unknown.

In conclusion, the totality of the currently available data regarding the potential benefits and risks of MOV support its use only as a second line agent for the treatment of mild-to-moderate COVID-19. Specifically, we recommend that MOV be authorized for the 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. FDA has also determined that the known and potential benefits of MOV, when used for the treatment of mild-to-moderate COVID-19 as described in Section III, outweigh the known and potential risks of the product. Therefore, the Review Division and the Office of Infectious Diseases conclude that the statutory criteria under section 564(c) of the Federal Food, Drug, and Cosmetic Act are met and recommend authorization of an EUA for MOV as described above.

In addition, to support an ongoing benefit/risk assessment of MOV use under the EUA, the Sponsor will be required to conduct several additional assessments, including a pregnancy surveillance program with mandated reporting by prescribers (provided the patient agrees to participate in the pregnancy surveillance program and allows the prescriber to disclose patient specific information to the Sponsor), an investigation into the inconsistent efficacy results in MK-

4482-002, a transgenic rodent germ cell gene mutation assay, and various clinical and nonclinical virology analyses as a condition of the authorization.

XXII. Considerations for Adverse Event Monitoring

This product will be used either in clinical trials under IND or in clinical practice under EUA. In clinical trials, FDA IND safety reporting regulations will apply. In clinical practice, EUA-labeled product will be made available. In the setting of a pandemic where practicing physicians will have many competing priorities, adverse event reporting under this EUA will be streamlined through the MEDWATCH system. The prescribing health care provider and/or the provider's designee will be responsible for mandatory reporting of all medication errors and all serious adverse events occurring during MOV use and considered potentially related to MOV within 7 calendar days from the health care provider's awareness of the event. The reports should include unique identifiers and the words "MOV use for COVID-19 under Emergency Use Authorization (EUA)."

XXIII. Mandatory and Discretionary Requirements for Use of the Product Under the EUA

Refer to the letter of authorization and the authorized Fact Sheet for Health Care Providers.

The review team provided the Office of the Assistant Secretary for Preparedness and Response with a checklist tool for prescribers that outlines all patient eligibility criteria and mandatory prescriber requirements. Use of the checklist tool is discretionary. The checklist may be provided to help states and sites manage the mandatory requirements for MOV use.

XXIV. Information To Be Conveyed to Health Care Providers and Recipients of the Product

The Sponsor's plan for distribution of the Fact Sheet for Health Care Providers and Fact Sheet for Patients and Caregivers is as follows:

- Each carton contains one bottle of forty 200 mg MOV tablets (one treatment course).
 - The fact sheets will include the global URL www.molnupiravir.com.
 - The carton has a QR code on it, which directs users to the Global URL www.molnupiravir.com. The global labeling site www.molnupiravir.com will allow users to select their country for country-specific information.

.....FDA agrees with the plan for implementation for dissemination of the following fact sheets:

- Fact Sheet for Health Care Providers (See Section [XXVII.3](#))
- Fact Sheet for Patients and Caregivers (See Section [XXVII.4](#))

XXV. Outstanding Issues/Data Gaps

Nonclinical

- Results of a pharmacokinetic (PK) study in wild-type Fisher 344 rats to establish if NHC or NHC-TP is detected in testes. The study should include plasma exposure levels that meet/exceed the human exposure for NHC. Results of the PK study will be submitted by March 2022.
- If the results of the PK study demonstrate NHC or NHC-TP distribution to testes, conduct a male germ cell mutation assay in the Big Blue[®] rat model. A protocol for the Big Blue[®] rat assay will be submitted no later than 30 days after the PK results are submitted to FDA (April 2022). Results from the Big Blue[®] rat assay will be submitted by July 2023.

Clinical

- Conduct a thorough investigation into the differences in efficacy observed in the first and second half of Part 2 of MK-4482-002. This assessment should involve the synthesis of data, including, but not limited to, the agreed upon additional baseline serology testing, a detailed comparison of baseline characteristics (including demographic, clinical disease, and virologic characteristics), and an exploration of potential differences in standard of care by region and over time. A preliminary report will be submitted by March 2022. The final report, including additional serology results, will be submitted by September 2022.

Clinical Virology

- Submit the complete viral shedding results and full genome SARS-CoV-2 nucleotide sequencing results from the full randomized population in MK-4482-002, Part 2. Viral sequencing analyses should include all baseline and end-of-treatment (Day 5) samples with sufficient RNA levels for analysis, as well as all post-treatment samples with viral RNA levels $\geq 100,000$ 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. Submissions should include summary report(s) and associated datasets (including analysis-ready datasets and raw fastq NGS data). A separate summary should be provided describing the results of the viral shedding and sequencing analyses specifically from immunocompromised patients.
- Evaluate the cell culture antiviral activity of MOV against an authentic SARS-CoV-2 isolate representative of the Omicron variant.
- Provide samples as requested of the authorized MOV to HHS for evaluation of activity against emerging global viral variants of SARS-CoV-2, including specific amino acid substitution(s) of interest (e.g., variants that are highly prevalent or that harbor substitutions in the target protein(s)) within 5 business days of any request made by HHS. Analyses performed with the supplied quantity of authorized MOV may include, but are not limited to, cell culture potency assays, biochemical assays, and in vivo efficacy assays.
- Establish a process for monitoring genomic database(s) for the emergence of global viral variants of SARS-CoV-2 and provide reports to the Agency on a monthly basis summarizing any findings as a result of its monitoring activities and as needed, any follow-up assessments planned or conducted.

- Assess the activity of the authorized MOV against any global SARS-CoV-2 variant(s) of interest (e.g., variants that are prevalent or becoming prevalent that harbor substitutions in the target protein or in protein(s) that interact with the target protein).

XXVI. References

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XXVII. Appendices

1. MK-4482-002, Part 1 Efficacy

The primary and secondary efficacy endpoints are the same for Part 1 of the trial as those for Part 2 of the trial, described above.

The proportion of participants who were hospitalized or died through Day 29 was comparable across intervention groups. No participant died and 11 participants were hospitalized through Day 29 ([Table 36](#)).

Table 36. Incidence of Death or Hospitalization Through Day 29, MK-4482-002, Part 1, mITT Population

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

Pairwise Comparison Among MK Treatment Groups	Unadjusted Difference	Adjusted Risk Difference % (95% CI) ^a	p-Value ^b
MOV 400 mg vs. MOV 200 mg	2.5	2.5 (-3.9, 9.8)	0.3351
MOV 800 mg vs. MOV 200 mg	2.7	2.7 (-3.7, 10.1)	0.3121
MOV 800 mg vs. MK-4482 400 mg	0.2	0.3 (-7.3, 8.3)	0.9342

Source: Clinical study report, Table 11-1

^a Adjusted differences, the corresponding confidence intervals and p-values are based on Miettinen & Nurminen method stratified by time of symptom onset (≤5 days, >5 days)

^b Nominal 2-sided p-value

Unknown Day 29 survival status is treated as failure

Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; MOV, molnupiravir

Post hoc subgroup analyses showed clinical benefit of MOV for participants with time to symptom onset within 5 days of randomization and at increased risk for severe disease (i.e., having at least one baseline risk factor; [Table 37](#)).

Table 37. Incidence of Hospitalization or Death Through Day for Participants With Symptom Onset ≥ 5 Days and at Increased Risk for Severe Disease, mITT Population

Treatment	N	n (%)	Treatment vs. Placebo	
			Risk Difference % (95% CI) ^a	p-Value ^b
MOV 200 mg	38	1 (2.6)	-9.1 (-24.5, 3.5)	0.1307
MOV 400 mg	38	2 (5.3)	-6.5 (-22.3, 7.5)	0.3224
MOV 800 mg	31	1 (3.2)	-8.5 (-24.1, 6.1)	0.2004
Placebo	34	4 (11.8)		
Pairwise Comparison Among MOV Treatment Groups			Risk Difference % (95% CI) ^a	p-Value ^b
MOV 400 mg vs. MOV 200 mg			2.6 (-9.0, 15.1)	0.5584
MOV 800 mg vs. MOV 200 mg			0.6 (-10.8, 14.0)	0.8845
MOV 800 mg vs. MK-4482 400 mg			-2.0 (-14.7, 11.7)	0.6820

Source: Clinical study report, Table 14.2-47

^a Adjusted differences, the corresponding confidence intervals and p-values are based on Miettinen & Nurminen method

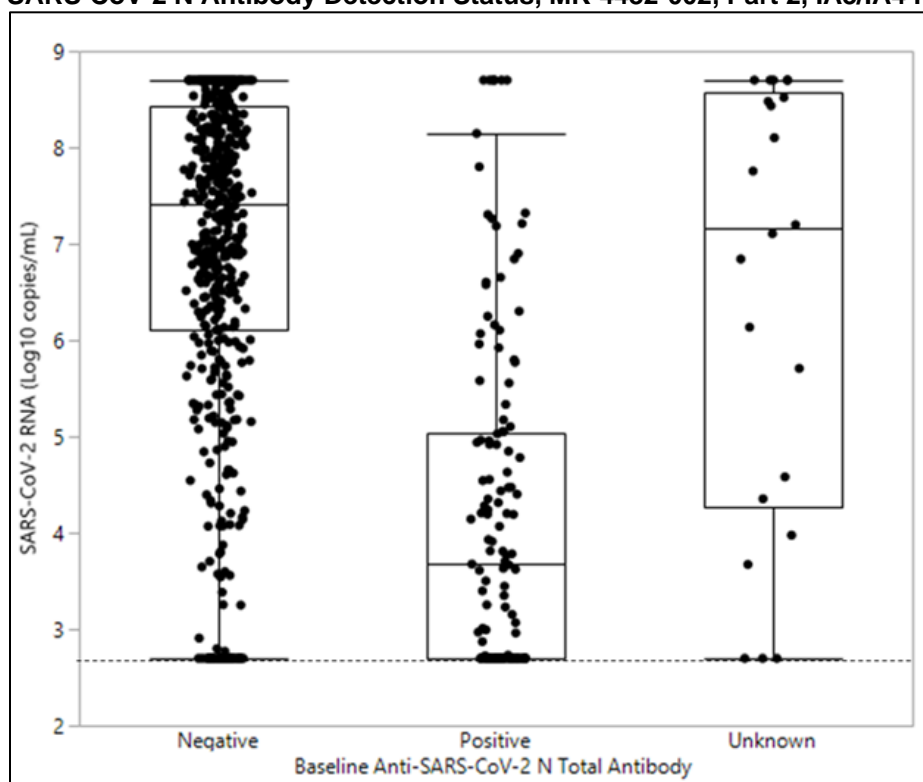
^b Nominal 2-sided p-value

Abbreviations: CI, confidence interval; mITT, modified intent-to-treat; MOV, molnupiravir

2. Additional Analyses by Baseline Serostatus, MK-4482-002, Part 2

Among participants with anti-SARS-CoV-2 N antibody detected at baseline, SARS-CoV-2 RNA levels in NP swabs were $\sim 4 \log_{10}$ copies/mL lower compared to those without detected baseline anti-SARS-CoV-2 antibody (Figure 6). Baseline anti-SARS-CoV-2 N antibody-positive participants showed reduced declines in NP viral RNA levels over time regardless of treatment arm, which is expected given the lower viral RNA levels at baseline.

Figure 6. SARS-CoV-2 RNA Levels in NP Swab Specimens at Baseline, According to Baseline Anti-SARS-CoV-2 N Antibody Detection Status, MK-4482-002, Part 2, IA3/IA4 Population



Source: FDA analysis

Abbreviations: IA3/IA4, interim analysis 3 and 4; NP, nasopharyngeal; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Presumably those who first developed anti-SARS-CoV-2 antibody as a result of the current infection would have more likely enrolled relatively later in the course of their infection. However, an analysis of time from symptom onset shows a comparable breakdown in both antibody-negative and antibody-positive participants ([Table 38](#)). These results could be interpreted to indicate that most of the positive baseline antibody results are a result of prior infection, not the early development of an antibody response as a result of the current infection.

Table 38. Breakdown of Time From Symptom Onset According to Baseline Anti-SARS-CoV-2 N Antibody Detection Status, MK-4482-002, Part 2, IA3/IA4 Population

Time From Symptom Onset	BL Anti-SARS-CoV-2 Aby Negative	BL Anti-SARS-CoV-2 Aby Positive
1	4% (24/586)	1% (2/139)
2	14% (83/586)	8% (11/139)
3	30% (177/586)	35% (48/139)
4	33% (192/586)	32% (44/139)
5	19% (110/586)	24% (34/139)
≤3 days	48% (284/586)	44% (61/139)
4-5 days	52% (302/586)	56% (78/139)

Source: FDA analysis

Abbreviations: Aby, antibody; BL, baseline; IA3/IA4, interim analysis 3 and 4; SARS-CoV-2, severe acute respiratory syndrome

Further analyses were conducted to assess the potential impact of baseline COVID-19 severity on treatment effect among participants who were seropositive at baseline. As shown in [Table 39](#) below, these analyses revealed that among participants with anti-SARS-CoV-2 antibodies and

mild COVID-19 at baseline, no treatment effect was observed. Among participants with baseline anti-SARS-CoV-2 antibodies present and moderate disease, no participants met the primary endpoint in either the MOV or placebo group. The finding that the rate of hospitalization or death was higher among antibody positive participants with mild COVID-19 than those with moderate COVID-19 in both arms is unexpected and may be attributable to the small size of each of these subgroups. The treatment effect in participants without baseline anti-SARS-CoV-2 antibodies was similar among those with mild and moderate COVID-19 at baseline.

Table 39. Incidence of Hospitalization or Death Through Day 29 by Baseline COVID-19 Severity and Anti-SARS-CoV-2 Baseline Antibody Status. MK-4482-002, Part 2

Baseline COVID-19 Severity and SARS-CoV-2 Baseline Antibody Serostatus	MOV 800 mg N=385 n/m (%)	Placebo N=377 n/m (%)	Difference (MOV – Placebo) % (95% CI)^a
Mild and antibody positive	2/40(5.0)	2/41 (4.9)	0.1 (-12.0, 12.4)
Mild and antibody negative	8/173 (4.6)	18/148 (12.2)	-7.5 (-14.3, -1.6)
Moderate and antibody positive	0/30 (0)	0/28 (0)	0 (-12.3, 11.5)
Moderate and antibody negative	15/125 (12.0)	30/138 (21.7)	-9.7, (-18.8, 0.6)

Source: Response to October 26, 2021, Information Request, Table 6

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

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

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; m, number of participants in the modified intent-to-treat population with the corresponding group; MOV, molnupiravir; N, total number of participants; n, number of participants died or hospitalized through Day 29; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

As was the case with MOV, vaccinated individuals were not represented in the trials supporting the authorizations of the monoclonal antibodies for similar intended uses. However, the monoclonal antibodies are authorized for use in outpatients at high risk for progression to severe COVID-19, including hospitalization or death, regardless of vaccination status. There are data available from an outpatient REGEN-COV clinical trial showing clinical benefit in both participants with a positive and negative baseline SARS-CoV-2 antibody status. Specifically, in a Phase 3 trial in high-risk outpatients with mild-to-moderate COVID-19 (COV-2067), among the subset of participants who were SARS-CoV-2 seropositive at baseline, there was a trend toward a decreased rate of COVID-19-related hospitalization or all-cause death through Day 29 among participants who received REGEN-COV 1200 mg compared to placebo and the relative risk reduction was similar in participants who were seropositive and seronegative at baseline (see Table 40).

These data supported the decision to authorize monoclonal antibodies for use in both vaccinated and unvaccinated individuals. Notably, similar data are not available from other outpatient monoclonal antibody programs, either because it was not collected or because the subgroup participants who were seropositive at baseline was too small to detect a benefit in the active treatment arm compared to the placebo arm.

Table 40. COVID-19-Related Hospitalization or All-Cause Death Through Day 29 by Baseline Serostatus in Trial COV-2067

Subpopulation	REGEN-COV 1200 mg Events/N (%)	Placebo Events/N (%)	Relative Risk Reduction (95% CI)
Baseline Seropositive	1/177 (0.6)	6/164 (3.7)	85% (NA, 98%)
Baseline Seronegative	3/500 (0.6)	18/519 (3.5)	83% (42%, 95%)

Source: (Weinreich et al. 2021)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; N, total number of participants; NA, not applicable

- 3. **Fact Sheet for Health Care Providers**
- 4. **Fact Sheet for Patients and Caregivers**
- 5. **PubMed Literature Search**

Not applicable

6. **Key Literature References**

See XXVI. References

7. **Other Review Elements**

Not applicable

8. **Pharmacometrics Review**

1. Population PK Analysis

1.1 Review Summary

In general, the Sponsor’s population PK analysis is considered acceptable for the purpose of descriptive labeling and covariate identification. The Sponsor’s analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in [Table 41](#).

Table 41. Specific Comments on Sponsor’s Final Population PK model

	Utility of the Final Model	Reviewer’s Comments
Support Sponsor’s proposed labeling statements about intrinsic and extrinsic factors	<p>“Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.”</p> <p>Pediatric Patients MOV has not been studied in pediatric patients.</p> <p>Patients With Renal Impairment Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild-to-moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m² or on dialysis.”</p>	<p>The statement is acceptable. Covariate analysis using the Sponsor’s basic model demonstrates that no evident difference (between 80-125%) exists based on age (in adults ≥18), sex, race, ethnicity, or disease severity (Figure 10).</p> <p>The magnitude of change in NHC CL in patients with mild and moderate renal impairment (6 and 22% decrease) was insufficient to warrant a dose adjustment in this population.</p>

Utility of the Final Model		Reviewer's Comments
Description of NHC Exposure	Table 3: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg Molnupiravir Every 12 Hours	
		NHC Geometric Mean (%CV)
	Pharmacokinetics in Patients	
	AUC _{0-12hr} (ng*hr/mL)*	8260 (41.0)
	C _{max} (ng/mL)*	2330 (36.9)
	C _{12hr} (ng/mL)*	31.1 (124)
	Pharmacokinetics in Healthy Subjects	
	AUC _{0-12hr} (ng*hr/mL)	8330 (17.9)
	C _{max} (ng/mL)	2970 (16.8)
	C _{12hr} (ng/mL)	16.7 (42.8)
	AUC Accumulation Ratio	1.09 (11.8)
	Absorption	
	T _{max} (hr) [†]	1.50 [1.00 – 2.02]
	Effect of Food	35% reduction in C _{max} , no effect on AUC
	Distribution	
Plasma Protein Binding (<i>in vitro</i>)	0%	
Apparent Volume of Distribution (L)*	142	
Elimination		
Effective t _{1/2} (hr)	3.3	
Apparent Clearance (L/hr)*	76.9	
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)	
*Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated		
†Values were obtained from population PK analysis.		

The table of NHC PK exposure estimates is acceptable. The model captures the central tendency of the data with low relative standard error. The reviewer was able to reproduce these numbers with no discordance.

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; CL, clearance; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; NHC, N3-hydroxycytidine; PK, pharmacokinetics; T_{max}, time to maximum plasma concentration; MOV, molnupiravir

1.2 Introduction

The primary objectives of the Sponsor's analysis were to

- develop a population PK model for MK-4482 using NHC plasma concentrations collected in Trials MK-4482-004, MK-4482-006, MK-4482-001, and MK-4482-002;
- identify and quantify the effects of intrinsic and extrinsic factors influencing the plasma PK of NHC; and
- predict metrics of exposures that will be used for parallel development of viral dynamics and exposure-response models.

1.3 Model Development

Data

The analyses were based on PK data from four studies. The study design, study population, and timing of blood samples varied among the four clinical studies. Brief descriptions of the studies included are presented in [Table 42](#) and [Table 43](#).

The final NONMEM data file for analysis contained 3754 PK observations from 571 participants. [Table 44](#) provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 42. Summary of Studies With PK Sampling Included in Population PK Analysis

Study Number/ Phase	Study Title	Participants	Duration of Dosing
MK-4482-P004 ^a / Phase 1	A Randomized, Double-Blind, Placebo-Controlled, First-in-Human Study Designed to Evaluate the Safety, Tolerability, and Pharmacokinetics of EIDD-2801 Following Oral Administration to Healthy Volunteers	Male or female adult healthy participants (N = 94 ^b)	SAD cohorts: 1 dose MAD cohorts: Q12h dosing on Days 1 to 5 and 1 dose on Day 6
MK-4482-P006 ^a / Phase 2a	A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability, and Efficacy of EIDD-2801 to Eliminate SARS-CoV-2 Viral RNA Detection in Persons with COVID-19	Male or female, symptomatic, adult outpatients with SARS-CoV-2 ^c (N = 22 ^b)	5 days
MK-4482-P001/ Phase 2/3	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Hospitalized Adults with COVID-19	Male or female, symptomatic, adult inpatients with SARS-CoV-2 ^d (N = 225 for Phase 2 + 500 for Phase 3 ^b)	5 days
MK-4482-P002/ Phase 2/3	A Phase 2/3, Randomized, Placebo-Controlled, Double-Blind Clinical Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of MK-4482 in Non-Hospitalized Adults with COVID-19	Male or female, symptomatic, adult outpatients with SARS-CoV-2 ^d (N = 225 for Phase 2 + 500 for Phase 3 ^b)	5 days

Source: Sponsor's Population PK Report, Table 1

Abbreviations: COVID-19, coronavirus disease 2019; MAD, multiple ascending dose; PK, pharmacokinetic; Q12H, every 12 hours; RNA, ribonucleic acid; SAD, single ascending dose; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Table 43. Summary of Dosing Regimens and PK Sampling Plans

Study Number/Phase	Dosing Regimen ^a	Pharmacokinetic Sampling Plan
MK-4482-P004 ^b / Phase 1	SAD: 8 cohorts of 6 participants receiving 1 dose under fasted conditions at 50, 100, 200, 400, 600, 800, 1200, and 1600 mg	Prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 24, 36, 48, and 72 h after dosing
	Food effect: 1 cohort of 6 participants receiving a 200-mg dose following a high-fat breakfast	Prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 24, 36, 48, and 72 h after dosing
	MAD: 7 cohorts of 6 participants receiving Q12h dosing at 50, 100, 200, 300, 400, 600, and 800 mg from Day 1 to Day 5 and 1 dose on Day 6	Day 1: prior to the 1st dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 h after the 1st dose Day 4: prior to the 1st dose Day 6: prior to the last dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 15, 24, 48, 72, and 192 h after the last dose
MK-4482-P006 ^b / Phase 2a	Q12h dosing at 200 mg over 5 days	Day 5: prior to dosing and approximately 1 h and 2 h after dosing
MK-4482-P001/ Phase 2/3	Phase 2: Q12h dosing at 200, 400, and 800 mg over 5 days	Phase 2: Prior to the 1st dose on Day 5, and 1, 3, 5, and 8 h after the 1st dose on Day 5
	Phase 3: Q12h dosing over 5 days; dose to be determined by interim analysis of Phase 2 data	Phase 3: Prior to the 1st dose on Day 5, and 1 h and 5 h after the 1st dose on Day 5
MK-4482-P002/ Phase 2/3		Phase 2: Prior to the 1st dose on Day 5, and 1.5 h after the 1st dose on Day 5 Phase 3: Prior to the 1st dose on Day 5, and 1.5 h after the 1st dose on Day 5

Source: Sponsor's Population PK Report, Table 2

Abbreviations: MAD, multiple ascending dose; PK, pharmacokinetic; Q12H, every 12 hours; SAD, single ascending dose

Table 44. Summary of Baseline Demographic Covariates for Analysis

Variable		MK-4482-P001 (n = 189)	MK-4482-P002 (n = 194)	MK-4482-P004 (n = 100)	MK-4482-P006 (n = 66)	Overall (n = 549)
Age (y)	Mean (SD)	56.3 (13.9)	48.8 (14.4)	38.8 (13.3)	41.2 (15.7)	48.7 (15.7)
	Median	56	50	35.5	37	50
	Min, Max	19, 91	18, 81	20, 60	19, 82	18, 91
Body Mass Index (kg/m ²)	Mean (SD)	30.2 (6.13)	29.7 (6.1)	24.8 (2.8)	27.3 (5.04)	28.7 (5.87)
	Median	28.9	29.7	25	27	27.7
	Min, Max	17.5, 48.8	18.1, 49.1	19, 29.9	19.8, 43.9	17.5, 49.1
Estimated Glomerular Filtration Rate (mL/min/1.73 m ²)	Mean (SD)	88.3 (24.7)	86 (19.2)	89.2 (16.3)	91 (19.5)	88 (20.9)
	Median	87.1	84.1	87.8	94	86.7
	Min, Max	32.2, 162	37, 147	56.9, 142	37.9, 128	32.2, 162
Body Weight (kg)	Mean (SD)	86.2 (20)	84 (18.4)	75.8 (10.8)	81 (18.4)	82.9 (18.2)
	Median	85	81.6	75.8	76.5	80.7
	Min, Max	50.7, 172	48, 134	48, 101	51, 131	48, 172
Sex, N (%)	Male	108 (57.1)	95 (49)	83 (83)	32 (48.5)	318 (57.9)
	Female	81 (42.9)	99 (51)	17 (17)	34 (51.5)	231 (42.1)
Racial Category, N (%)	White or Caucasian	139 (73.5)	145 (74.7)	93 (93)	56 (84.8)	433 (78.9)
	Black or African American	7 (3.7)	14 (7.22)	4 (4)	5 (7.58)	30 (5.46)
	American Indian or Alaska Native	4 (2.12)	5 (2.58)	0 (0)	0 (0)	9 (1.64)
	Native Hawaiian or other Pacific Islander	1 (0.529)	0 (0)	0 (0)	0 (0)	1 (0.182)
	Asian	18 (9.52)	1 (0.515)	0 (0)	2 (3.03)	21 (3.83)
	Other	20 (10.6)	29 (14.9)	3 (3)	3 (4.55)	55 (10)
Ethnicity, N (%)	Non-Hispanic or Latino	117 (61.9)	131 (67.5)	99 (99)	44 (66.7)	391 (71.2)
	Hispanic or Latino	72 (38.1)	63 (32.5)	1 (1)	22 (33.3)	158 (28.8)
Geographic Region, N (%)	North America	26 (13.8)	66 (34)	0 (0)	66 (100)	158 (28.8)
	Europe	98 (51.9)	88 (45.4)	100 (100)	0 (0)	286 (52.1)
	Asia Pacific	9 (4.76)	0 (0)	0 (0)	0 (0)	9 (1.64)
	Latin America	56 (29.6)	34 (17.5)	0 (0)	0 (0)	90 (16.4)
	Africa	0 (0)	6 (3.09)	0 (0)	0 (0)	6 (1.09)

Variable		MK-4482-P001 (n = 189)	MK-4482-P002 (n = 194)	MK-4482-P004 (n = 100)	MK-4482-P006 (n = 66)	Overall (n = 549)
Hepatic Function Category (Modified Child-Pugh Criteria), N (%)	Normal function	146 (77.2)	191 (98.5)	100 (100)	63 (95.5)	500 (91.1)
	Mild impairment	41 (21.7)	2 (1.03)	0 (0)	3 (4.55)	46 (8.38)
	Moderate impairment	2 (1.06)	1 (0.515)	0 (0)	0 (0)	3 (0.546)
Hepatic Function Category (Modified NCI Criteria), N (%)	Normal function	177 (93.7)	190 (97.9)	100 (100)	66 (100)	533 (97.1)
	Mild impairment	12 (6.35)	4 (2.06)	0 (0)	0 (0)	16 (2.91)
Renal Function Category, N (%)	Normal function	84 (44.4)	83 (42.8)	47 (47)	36 (54.5)	250 (45.5)
	Mild impairment	80 (42.3)	97 (50)	52 (52)	27 (40.9)	256 (46.6)
	Moderate impairment	25 (13.2)	14 (7.22)	1 (1)	3 (4.55)	43 (7.83)
Formulation, N (%)	Oral solution	0 (0)	0 (0)	36 (36)	0 (0)	36 (6.56)
	Capsule	189 (100)	194 (100)	64 (64)	66 (100)	513 (93.4)
Hospitalization Status, N (%)	Healthy	0 (0)	0 (0)	100 (100)	0 (0)	100 (18.2)
	Non-hospitalized	0 (0)	194 (100)	0 (0)	66 (100)	260 (47.4)
	Hospitalized	189 (100)	0 (0)	0 (0)	0 (0)	189 (34.4)
Baseline Disease Severity, N (%)	Healthy	0 (0)	0 (0)	100 (100)	0 (0)	100 (18.2)
	Mild	25 (13.2)	82 (42.3)	0 (0)	0 (0)	107 (19.5)
	Moderate	82 (43.4)	112 (57.7)	0 (0)	0 (0)	194 (35.3)
	Severe	82 (43.4)	0 (0)	0 (0)	0 (0)	82 (14.9)
	Missing	0 (0)	0 (0)	0 (0)	66 (100)	66 (12)
High Risk of Severe Illness, N (%)	No	0 (0)	52 (26.8)	100 (100)	27 (40.9)	179 (32.6)
	Yes	0 (0)	142 (73.2)	0 (0)	39 (59.1)	181 (33)
	Missing	189 (100)	0 (0)	0 (0)	0 (0)	189 (34.4)
Baseline Remdesivir Use, N (%)	No	141 (74.6)	194 (100)	0 (0)	66 (100)	401 (73)
	Yes	48 (25.4)	0 (0)	0 (0)	0 (0)	48 (8.74)
	Missing	0 (0)	0 (0)	100 (100)	0 (0)	100 (18.2)

Source: Sponsor's Population PK Report, Table 5

Abbreviations: N, number of participants; NCI, National Cancer Institute; SD, standard deviation

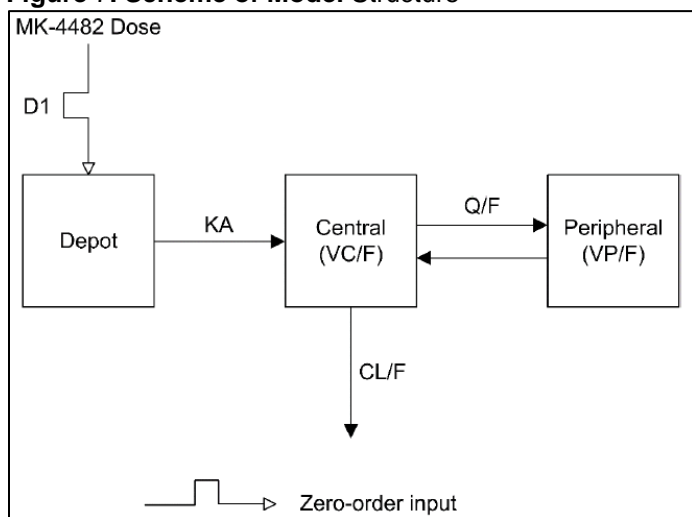
Base Model

The final base model was a two-compartment PK model with saturable absorption, and first-order elimination from the central compartment. The effect of weight was estimated as an allometric exponent on CL/F and also for BMI on Vc/F. Sex was included as a factor on Vc/F, and the effect of food was included on D1 ([Figure 7](#)).

Interindividual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Additive models on ln-transformed dependent variable were investigated as well. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value (OFV),

accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Figure 7. Scheme of Model Structure



Source: Sponsor's Population PK Report, Figure 11

Abbreviations: CL, clearance; F, bioavailability; KA, absorption rate constant; Q, organ blood flow; VC, volume of central compartment; VP, volume of peripheral compartment

Reviewer's Comments

The Sponsor's use of a zero-order input to the depot compartment is somewhat atypical but applied to account for limitations of trying to fit the base model that was identified in healthy patients to all of the population PK data. The Sponsor was unable to achieve model convergence with full dataset and sought to use zero-order input to a depot for reasons of parsimony.

Covariate Analysis

Covariate parameters shown in [Table 45](#) were added to the base model using forward inclusion. Graphical analysis, clinical judgment, physiologic relevance, and mechanistic plausibility were used to determine which covariates should be tested with the various PK parameters. Additionally, collinearity of covariates was assessed to ensure that no collinear covariates were added to the model.

Table 45. Planned Covariate Analyses

Covariate	Absorption Terms	Elimination Terms	Volume Terms	NHC to NHC-TP Transformation Terms
Body Weight	X	X	X	X
Body Mass Index	X	X	X	X
Age		X	X	X
Sex		X	X	X
Racial Classification	X	X	X	X
Ethnicity	X	X	X	X
Geographic Region	X	X	X	X
Fed Status	X			
SARS-CoV-2 Status	X	X	X	X
Hospitalization	X	X	X	X
Illness Severity	X	X	X	X
eGFR		X		
Baseline Remdesivir Use		X	X	

Source: Sponsor's Population PK Report, Table 3

Abbreviations: eGFR, estimated glomerular filtration rate; NHC-TP, N3-hydroxycytidine triphosphate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

1.4 Final Model

The parameter estimates for the final covariate model are listed in [Table 46](#). The goodness-of-fit plots for the final covariate model for all data are shown in [Figure 8](#). The Visual Predictive Check (VPC) plot for the final covariate model with all data is shown in [Figure 9](#).

Table 46. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

Parameter		Final Parameter Estimate		Magnitude of Variability	
		Population Mean	%RSE	Final Estimate	%RSE
CL/F	Apparent central clearance in 80-kg participants (L/h)	76.9	2.01	41.1 %CV	14.9
	Power of body weight effect (-)	0.421	20.4		
VC/F	Apparent central volume in 28-kg/m ² BMI male participants (L)	72.0	6.40	40.0 %CV	35.8
	Proportional shift in female participants (-)	-0.313	18.1		
	Power of BMI effect (-)	0.753	28.4		
Q/F	Apparent distribution clearance (L/h)	3.35	6.73	NE	NA
VP/F	Apparent peripheral volume (L)	70.0	14.8	NE	NA
KA	First-order absorption rate constant (1/h)	0.830	2.81	NE	NA
D1	Zero-order absorption duration (h)	0.802	4.83	42.8 %CV	15.9
	Proportional shift due to high-fat meal (-)	5.68	10.4		
	Proportional shift in oral solution (-)	-0.644	5.71		
	Proportional shift in hospitalized patients (-)	-0.265	22.4		
PHF	Probability of unknown high-fat meal (-)	0.250	FIXED	NE	NA
Residual Variability in Phase 1 Studies		0.123	9.58	35.1 %CV	NA
Residual Variability in Phase 2 Studies		0.268	5.33	51.7 %CV	NA
Minimum Value of the Objective Function = 38916.167					

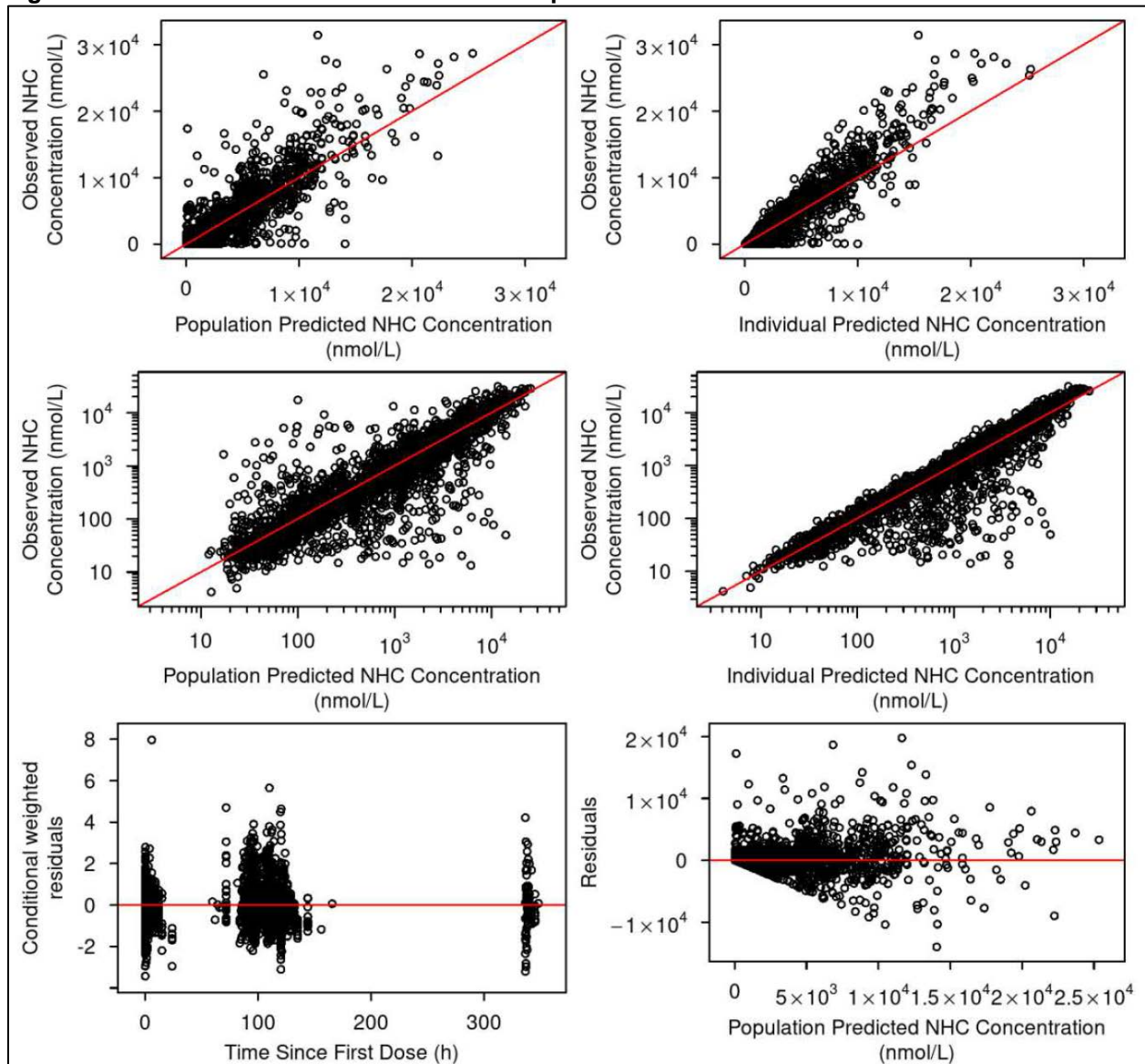
Abbreviations: BMI, body mass index; %CV, coefficient of variation expressed as a percent; IIV, interindividual variability; NA, not applicable; NE, not estimated; NHC, β -d-N4-hydroxycytidine; %RSE, relative standard error expressed as a percent.

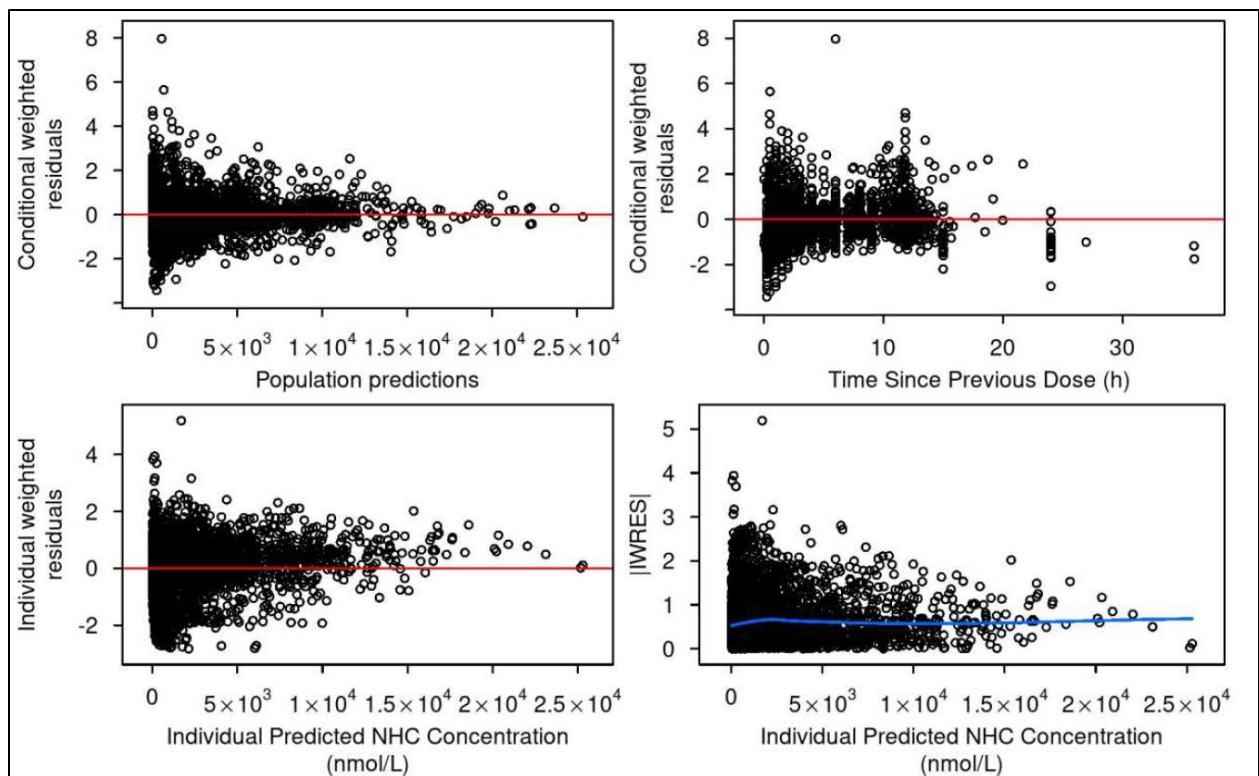
Note: Shrinkage estimates: 9.0% for IIV in CL/F, 36.6% for IIV in VC/F, and 39.0% for IIV in D1.

Source: Sponsor's Population PK Report, Table 13

Abbreviations: CI, confidence interval; CL, clearance; F, bioavailability; KA, absorption rate constant; Q, organ blood flow; VC, volume of central compartment; VP, volume of peripheral compartment

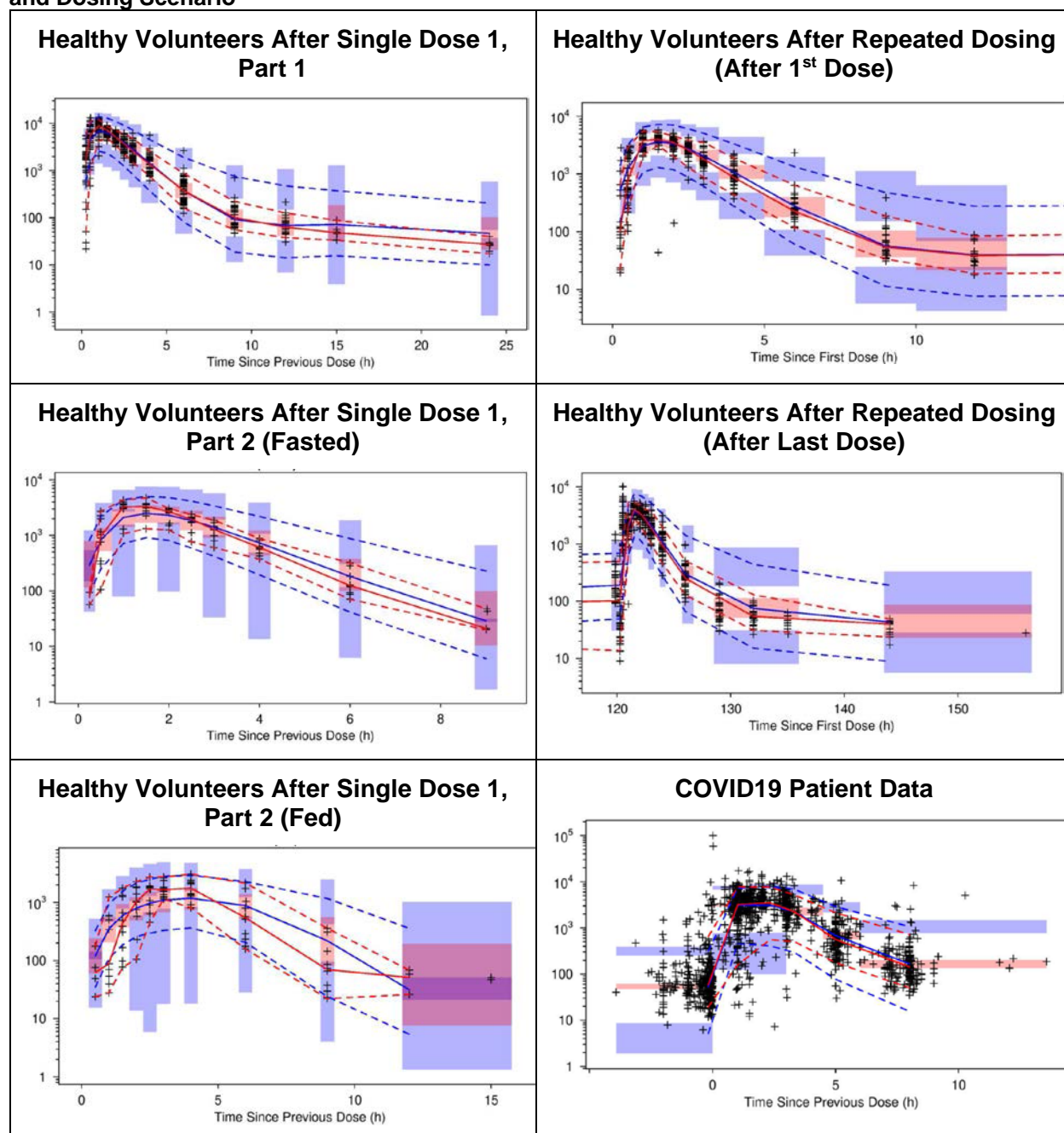
Figure 8. Goodness-of-Fit Plots for the Final Population PK Model





Source: Sponsor's Population PK Report, Figure 15
 Abbreviations: NHC, N3-hydroxycytidine; PK, pharmacokinetic

Figure 9. Prediction Corrected VPC Plots for the Final Population PK Model by Patient Population and Dosing Scenario



Data: + Observations
 — Median — 5th and 95th percentiles
Predictions: — Median — 5th and 95th percentiles
 ■ 95% CI of prediction percentiles

Medians and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose interval.

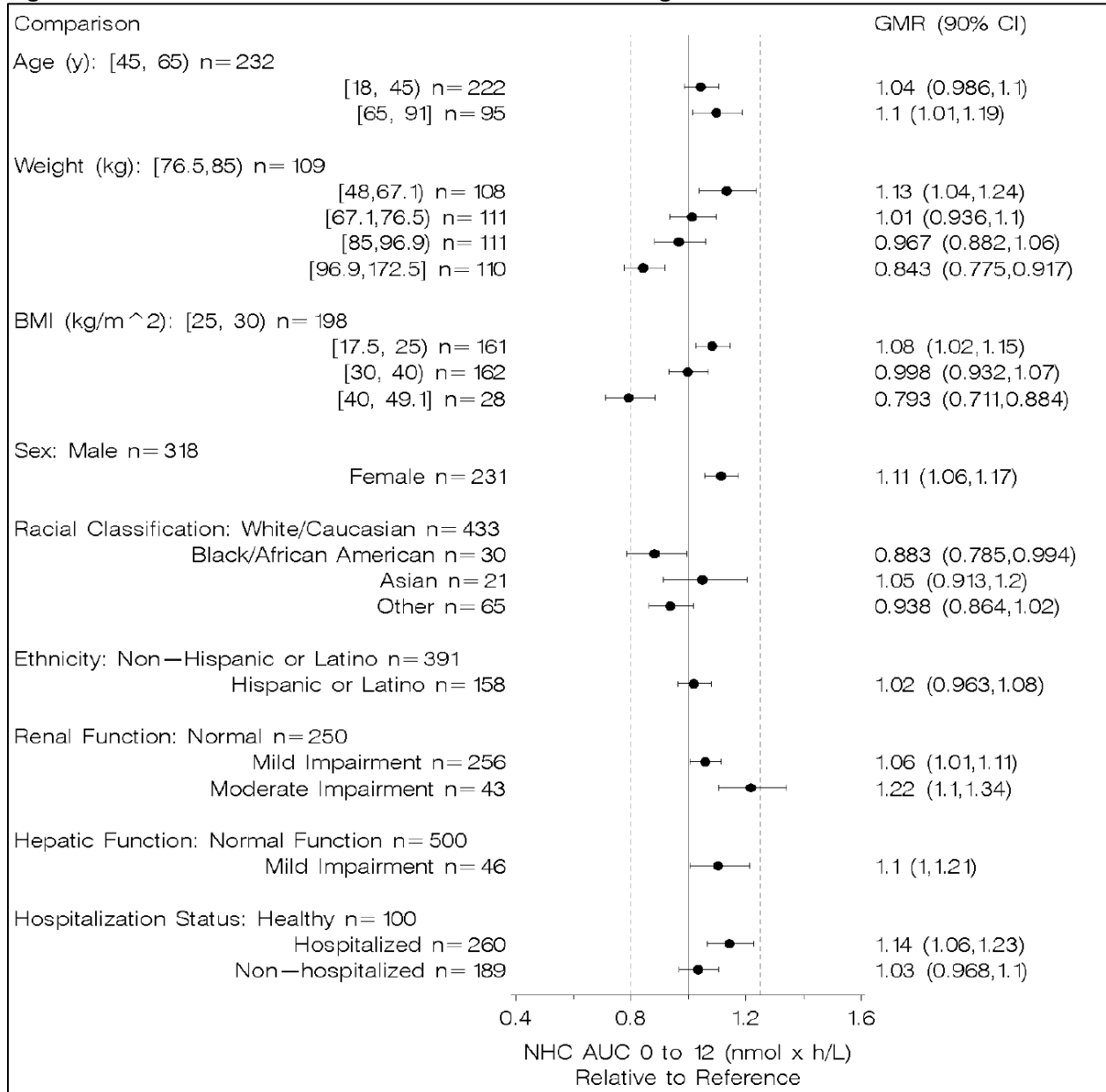
Source: Sponsor's Population PK Report, Figure 17–19

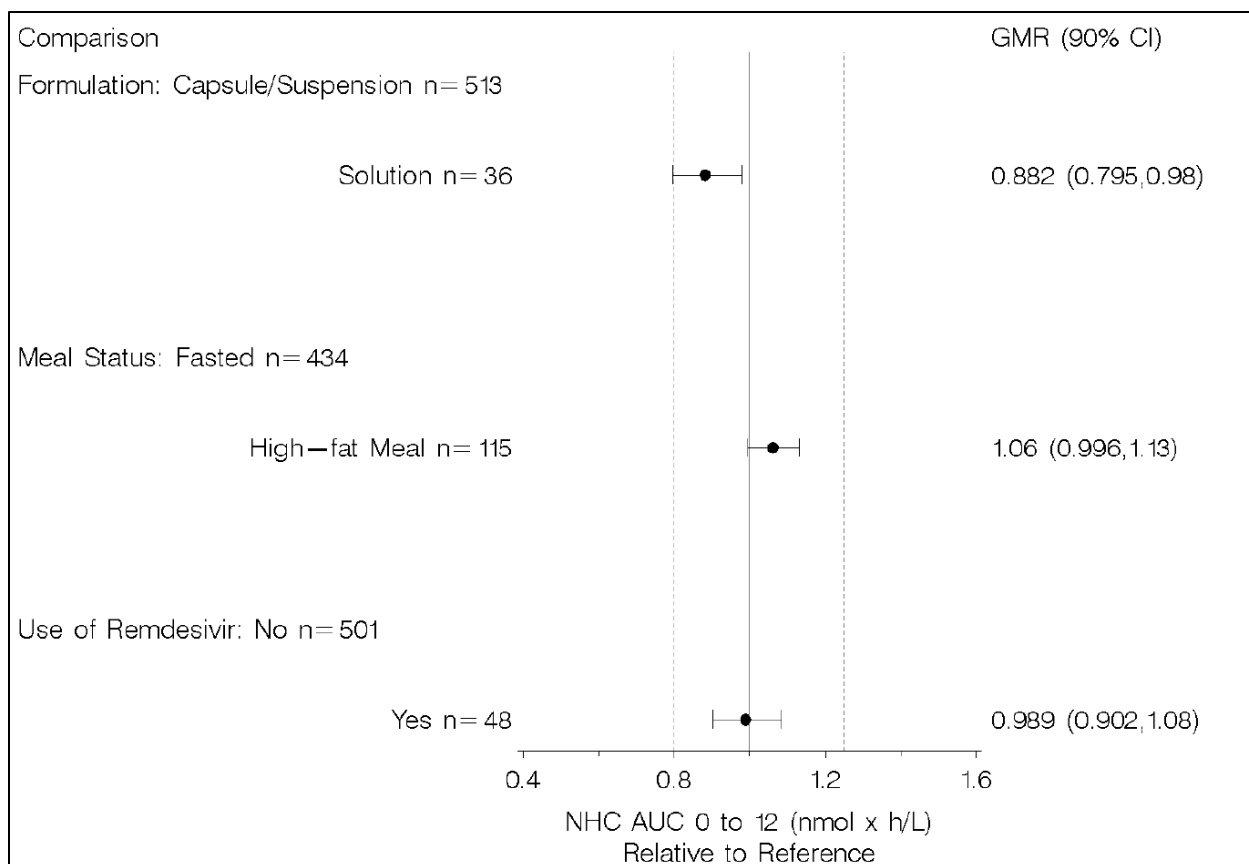
Y-axis Indicates NHC Concentrations

Abbreviations: CI, confidence interval; NHC, N3-hydroxycytidine; PK, pharmacokinetic; VPC, visual predictive check

The effects of various intrinsic and extrinsic factors on MOV AUC_{0-12h} are depicted in [Figure 10](#).

Figure 10. Covariate Effects on AUC₀₋₁₂ of NHC After 800 mg MOV BID





Source: Sponsor's Population PK Report, Figure 27

Abbreviations: AUC, area under the curve; BID, twice daily; CI, confidence interval; GMR, geometric mean ratio; MOV, molnupiravir; NHC, N3-hydroxycytidine

Reviewer's Comments

The Sponsor's covariate analysis suggests that the statements regarding no effect of age (in adults ≥ 18), sex, race, ethnicity, or disease severity on NHC, in the fact sheet, are acceptable. Additionally, the conclusions that mild-to-moderate renal impairment, body weight, BMI did not have clinically meaningful effects on NHC exposure is also acceptable. See further discussion regarding the Sponsor's exposure-response analyses. The Sponsor's assessment of hepatic impairment predominantly included those with normal hepatic function (n=500) and those with mild hepatic impairment (n=46). That being said, mild hepatic impairment did not have a significant effect on MOV clearance.

1.5 Summary of NHC Pharmacokinetic Exposures

The Sponsor applied the final population PK model with the corresponding individual Bayesian estimates to simulate NHC exposures after 5 days of dosing 800 mg BID MOV for every participant included in population PK dataset. Secondary PK parameters of C_{max} , C_{trough} , and AUC_{0-12} of NHC are shown in [Table 47](#).

Table 47. Model Predicted NHC Plasma Exposures After the Last Dose of 800 mg BID

Variable		MK-4482-P001	MK-4482-P002	MK-4482-P004	MK-4482-P006	Overall	Patients With COVID-19 ^a
Maximum Concentration (nmol/L)	Mean (SD)	9530 (3110)	NA ^b	10600 (2140)	NA ^b	9910 (2840)	9530 (3110)
	Geom. mean (%CV)	8990 (36.9)		10400 (20.7)		9460 (32.6)	8990 (36.9)
	Median	9260		10600		9870	9260
	P5, P95	4580, 15600		7570, 14800		5050, 15400	4580, 15600
	n	178		100		278	178
Trough Concentration (nmol/L)	Mean (SD)	230 (555)	413 (1470)	102 (69.1)	185 (472)	266 (954)	302 (1050)
	Geom. mean (%CV)	110 (123)	132 (141)	87.7 (55.7)	117 (73)	113 (113)	120 (124)
	Median	88.9	102	83.2	102	95.6	97.9
	P5, P95	34.5, 860	41.8, 1280	42.3, 284	59.4, 286	39.2, 582	39.2, 860
	n	189	194	100	66	549	449
AUC ₀₋₁₂ (nmol x h/L)	Mean (SD)	32500 (16100)	38000 (30100)	29800 (6880)	34600 (12900)	34200 (21100)	35200 (23000)
	Geom. mean (%CV)	30100 (38)	33200 (46.9)	29100 (22.3)	33200 (27.6)	31300 (38.3)	31900 (41)
	Median	28800	30800	28700	32100	29900	30200
	P5, P95	18800, 56800	19600, 80900	20600, 39800	24400, 49100	19600, 56800	19500, 65200
	n	189	194	100	66	549	449

Abbreviations: AUC₀₋₁₂, area under the NHC concentration versus time curve from 0 to 12 h postdose; C_{max}, maximum NHC concentration; %CV, coefficient of variation expressed as a percent; Geom., geometric; n, number of participants; NA, not applicable; NHC, β-d-N4-hydroxycytidine; Px, xth percentile; SD, standard deviation.

^a Excludes data from Study MK-4482-P004.

^b C_{max} distribution was assessed based upon the subset of the analysis population in which the absorption peak could be reliably described.

Source: Sponsor's Population PK Report, Figure 17–19

Abbreviations: BID, twice daily; COVID-19, coronavirus disease 2019; MOV, molnupiravir; PK, pharmacokinetic

Reviewer's Comments

The Sponsor's model appears reasonably unbiased based on the above goodness of fit plots ([Figure 8](#) and [Figure 9](#)) for describing the PK of NHC. The values in [Table 47](#) were reproduced and are acceptable for labeling purposes.

2. Exposure-Response for Secondary Virologic Efficacy Endpoints

The Sponsor performed exposure-response for the virologic endpoints in Trials MK-4482-001 and MK-4482-002. The evidence shown in these exposure response relationships is supportive of using the 800 mg dose.

The analyses were performed with data from both MK-4482-001 and MK-4482-002 for the following three virologic endpoints:

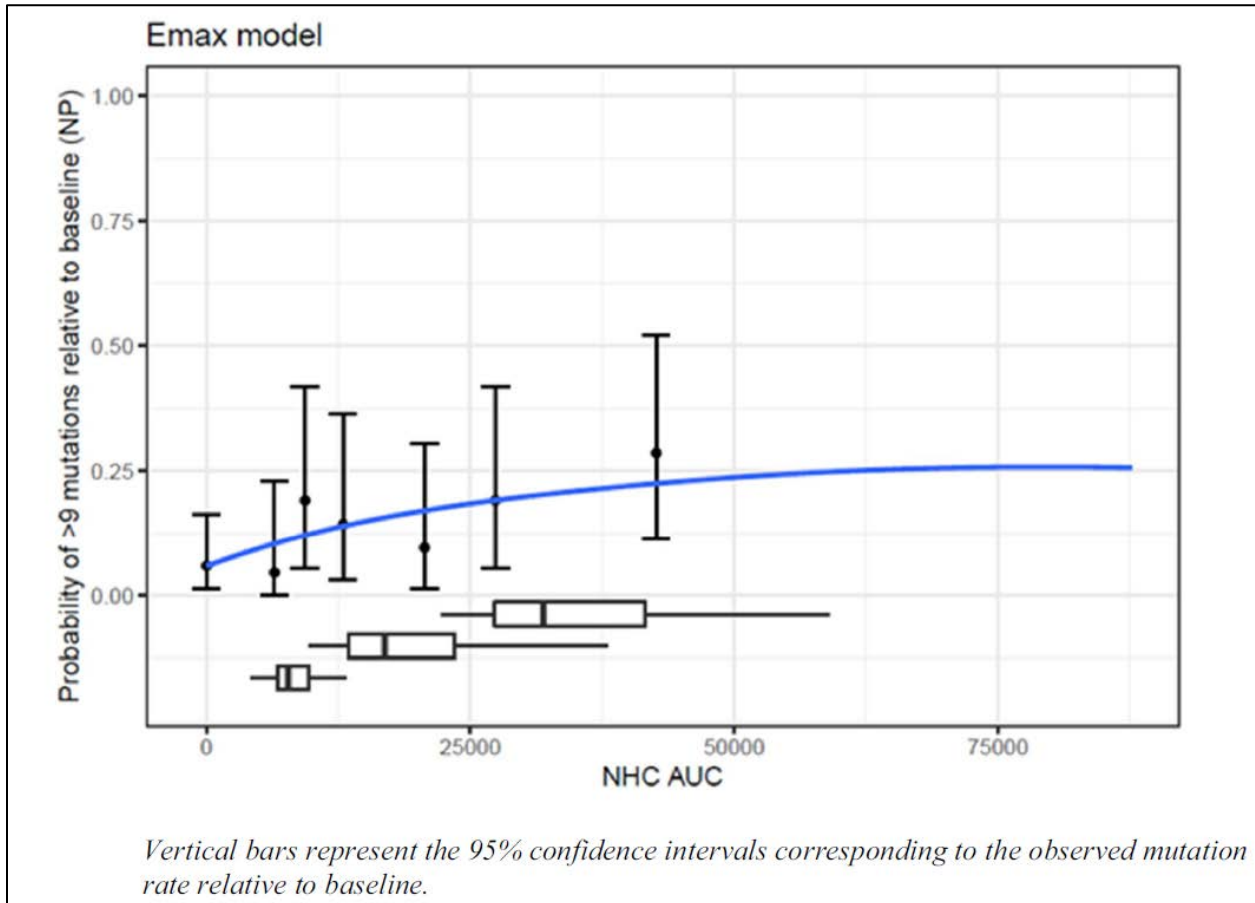
- Probability of mutation rate >9 per 10,000 bases relative to baseline
- Viral load change from baseline
- Probability of undetectable viral load on Day 29

Mutation Rate Relative to Baseline

Data from patients in Trials MK-4482-001 and MK-4482-002 revealed 2/22 (9%), 4/25 (16%), 3/24 (13%), and 9/18 (50%) participants in the placebo, 200, 400, and 800 mg groups, respectively, had >9 nucleotide mutations per 10,000 bases suggesting the presence of a dose-response relationship. Exposure-response analysis (logistic regression) of the mutation rate data identified a trend (p=0.10) at >3 and >6 thresholds and a significant relationship (unadjusted p-value of <0.05) at the >9 threshold (number of nucleotide mutations per 10,000 bases across the viral genome (30,000 bases), compared to the baseline (Day 1) sequence).

The Sponsor concluded that “Mutation rate exposure-response relationship was best described by Emax logistic regression models, which indicate that the drug effect may be saturating at exposures in the range of the 800 mg dose based on the estimated plateau that is apparent in [Figure 11](#).”

Figure 11. Logistic Regression Relationship for Probability of Mutation Rate >9 per 10,000 Base Pairs Relative to Baseline

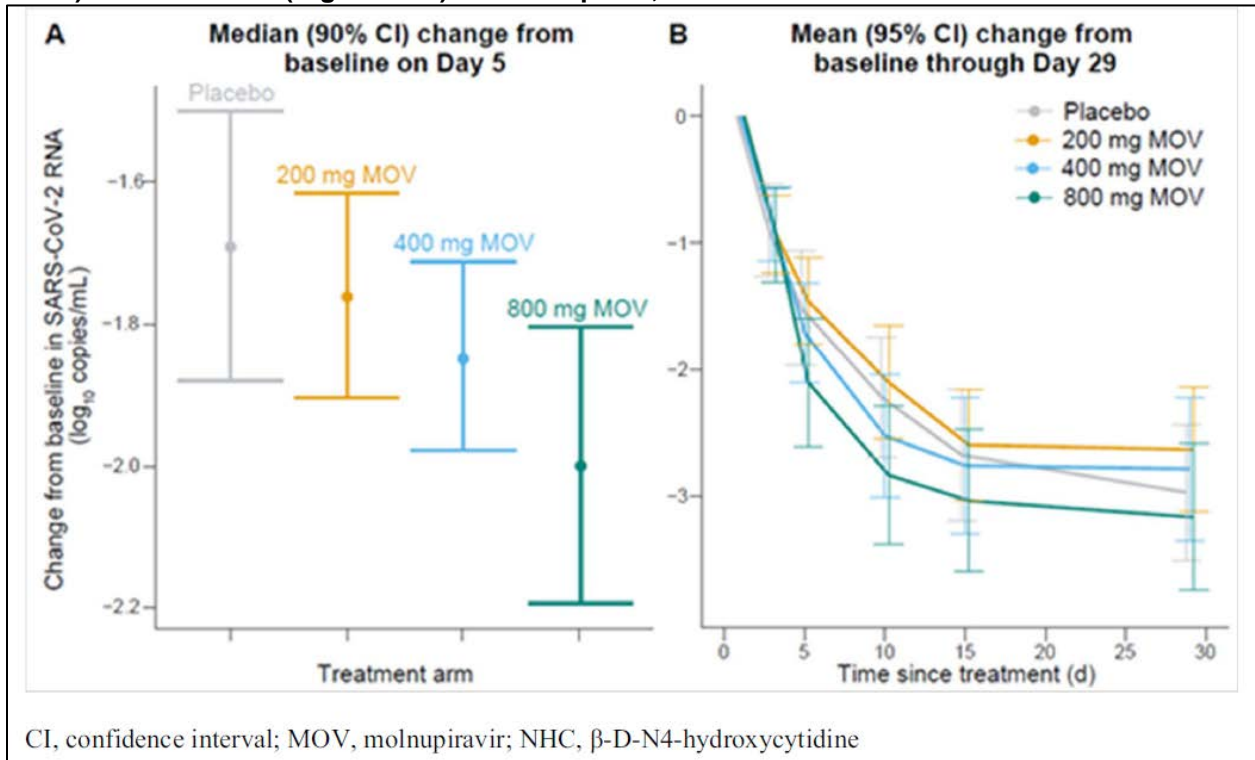


Source: Sponsor's EUA Application Report, Figure 13
Abbreviations: AUC, area under the curve; NHC, N3-hydroxycytidine

Viral Load Change From Baseline and Probability of Undetectable Viral Load on Day 29

The Sponsor's viral load data by dose in Trials MK-4482-001 and MK-4482-002 suggest 800 mg provides the most reduction in SARS-CoV-2 RNA copies when compared to placebo, 200, and 400 mg dose levels (Figure 12 and Figure 13).

Figure 12. Viral Dynamic Model Relationship Between MOV Dose and Viral Load on Day 5 (Left Panel) and Over Time (Right Panel) for Participants, MK-4482-001 and MK-4482-002

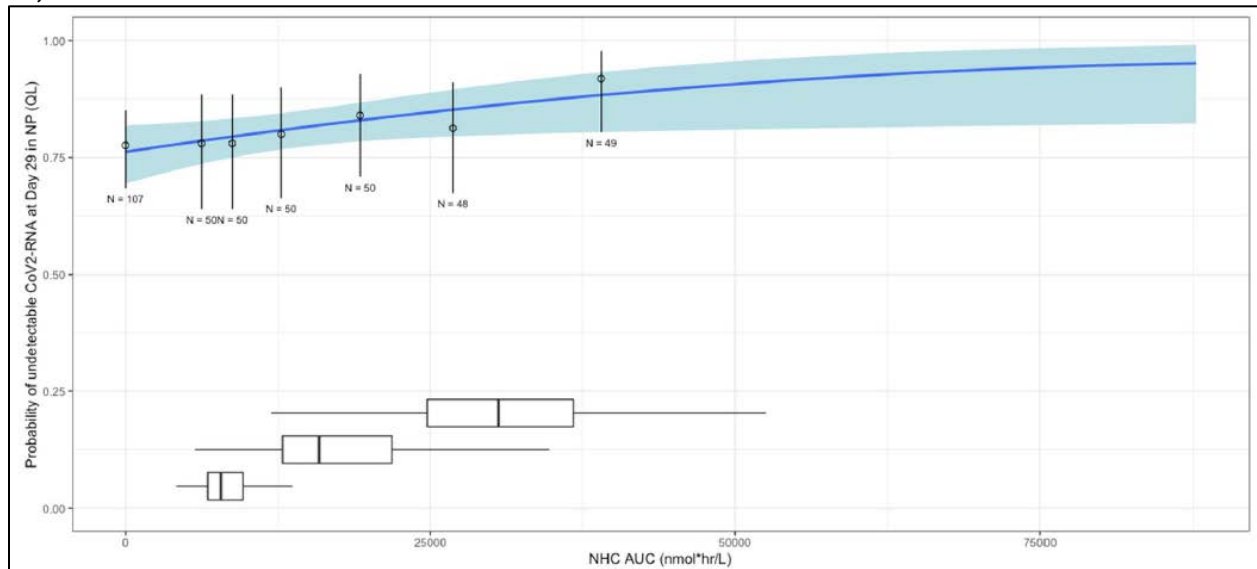


Source: Sponsor's EUA Application Report, Figure 14

Note: Data are included for patients where the time since symptom onset was ≤5 days

Abbreviations: RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure 13. Logistic Regression Relationship for the Probability of Undetectable Viral Load on Day 29, MK-4482-001 and MK-4482-002



Note: Pred Prob (95% CI): lowess of the predicted probability and 95% CI (to smooth out influence of exposure);
 Obs: Open symbols representing the observed proportion of subjects with undetectable RNA for each sextile of exposure, plotted at the median of the sextile;
 Vertical bars representing the 95% exact confidence intervals corresponding to the observed proportion of subjects with undetectable RNA;
 Boxplots show the distribution of exposures at different dose levels

Source: Sponsor's EUA Application Report, Figure 15

Abbreviations: AUC, area under the curve; CI, confidence interval; COV-2, coronavirus 2; NHC, N3-hydroxycytidine; RNA, ribonucleic acid

Based on the Sponsor's dose- and exposure-response assessments, the 800 mg dose of MOV appears to yield the greatest virologic response of the studied treatments.

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR MOLNUPIRAVIR

HIGHLIGHTS OF EMERGENCY USE AUTHORIZATION (EUA)
These highlights of the EUA do not include all the information needed to use molnupiravir under the EUA. See the FULL FACT SHEET FOR HEALTHCARE PROVIDERS for molnupiravir.

MOLNUPIRAVIR capsules, for oral use
Original EUA Authorized Date: 12/2021

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER EMERGENCY USE AUTHORIZATION

Refer to FULL FACTSHEET for details.

-----EUA FOR MOLNUPIRAVIR-----

The U.S. Food and Drug Administration (FDA) has issued an EUA for the emergency use of the unapproved molnupiravir, a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis 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 progressing 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. Molnupiravir is not FDA-approved for any use including for use for the treatment of COVID-19. Prior to initiating treatment with molnupiravir, carefully consider the known and potential risks and benefits. (1)

LIMITATIONS OF AUTHORIZED USE (1)

- Molnupiravir is not authorized
 - for use in patients less than 18 years of age (5.2)
 - for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19. (2.1)
 - for use for longer than 5 consecutive days.
 - for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

Molnupiravir is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of molnupiravir under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

See the box in the beginning of the Full Fact Sheet for details on mandatory requirements for administration of molnupiravir under emergency use authorization.

See Full Fact Sheet for Healthcare Providers for the justification for emergency use of drugs during the COVID-19 pandemic, information on available alternatives, and additional information on COVID-19.

-----DOSAGE AND ADMINISTRATION-----

- 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food. (2.1)

- Take molnupiravir as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset. (2.1)
- Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2. (2.1)
- Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established. (2.1)

-----DOSAGE FORMS AND STRENGTHS-----

Capsules: 200 mg (3)

-----CONTRAINDICATIONS-----

No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA. (4)

-----WARNINGS AND PRECAUTIONS-----

- Embryo-Fetal Toxicity: Molnupiravir is not recommended for use during pregnancy. (5.1, 8.1, 8.3)
- Bone and Cartilage Toxicity: Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. (5.2, 8.4, 13.2)

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence \geq 1%) are diarrhea, nausea, and dizziness. (6.1)

You or your designee must report all SERIOUS ADVERSE EVENTS or MEDICATION ERRORS potentially related to molnupiravir (1) by submitting FDA Form 3500 [online](#), (2) by [downloading](#) this form and then submitting by mail or fax, or (3) contacting the FDA at 1-800-FDA-1088 to request this form. Please also provide a copy of this form to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-800-672-6372 or Fax 215-616-5677 (6.4)

-----DRUG INTERACTIONS-----

No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA. (7)

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: The use of molnupiravir is not recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir. (8.1, 8.3)
- Lactation: Breastfeeding is not recommended during treatment and for 4 days after the last dose of molnupiravir. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir. (8.2)

See FACT SHEET FOR PATIENTS AND CAREGIVERS.

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FULL FACT SHEET FOR HEALTHCARE PROVIDERS

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF MOLNUPIRAVIR UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of molnupiravir, the following steps are required. Use of molnupiravir under this EUA is limited to the following (all requirements must be met):

1. 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 [see *Limitations of Authorized Use (1)*].
2. As the prescribing healthcare provider, review the information contained within the “Fact Sheet for Patients and Caregivers” with your patient or caregiver prior to the patient receiving molnupiravir. Healthcare providers must provide the patient/caregiver with an electronic or hard copy of the “Fact Sheet for Patients and Caregivers” prior to the patient receiving molnupiravir and must document that the patient/caregiver has been given an electronic or hard copy of the “Fact Sheet for Patients and Caregivers”.
3. The prescribing healthcare providers must inform the patient/caregiver that:
 - i. Molnupiravir is an unapproved drug that is authorized for use under this Emergency Use Authorization.
 - ii. There are no adequate, approved, available products for the treatment of COVID-19 in adults who have mild-to-moderate COVID-19 and are at high risk for progressing to severe COVID-19, including hospitalization or death.
 - iii. Other therapeutics are currently authorized for the same use as molnupiravir. For additional information on all products authorized for treatment or prevention of COVID-19, please see <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.
 - iv. There are benefits and risks of taking molnupiravir as outlined in the “Fact Sheet for Patients and Caregivers.”
 - v. Merck Sharp & Dohme has established a pregnancy surveillance program.
 - vi. Females of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.
 - vii. Males of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose.
4. The prescribing healthcare provider must assess whether a female of childbearing potential is pregnant or not, if clinically indicated [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.3)*].
5. Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. If molnupiravir is used during pregnancy, prescribing healthcare providers must communicate to the patient the known and potential benefits and the potential risks of molnupiravir use during pregnancy, as outlined in the “Fact Sheet for Patients and Caregivers” [see *Warnings and Precautions (5.1, 5.2)*, *Use in Specific Populations (8.1, 8.3)* and *Nonclinical Toxicology (13.1)*].

6. If the decision is made to use molnupiravir during pregnancy, the prescriber must document that the known and potential benefits and the potential risks of molnupiravir use during pregnancy, as outlined in the “Fact Sheet for Patients and Caregivers,” were discussed with the patient.
7. The prescribing healthcare provider must document that a pregnant individual was made aware of Merck Sharp & Dohme’s pregnancy surveillance program at 1-877-888-4231 or pregnancyreporting.msd.com.
 - a. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient’s name and contact information to Merck Sharp & Dohme.
8. The prescribing healthcare provider and/or the provider’s designee is/are responsible for mandatory reporting of all medication errors and serious adverse events potentially related to molnupiravir within 7 calendar days from the healthcare provider’s awareness of the event [see *Adverse Reactions* (6.4)].

For information on clinical studies of molnupiravir and other therapies for the treatment of COVID-19, see www.clinicaltrials.gov.

1 EMERGENCY USE AUTHORIZATION

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product molnupiravir for treatment of mild-to-moderate COVID-19 in adults:

- with positive results of direct SARS-CoV-2 viral testing, and
- who are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website¹ for additional details, and for
- whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

LIMITATIONS OF AUTHORIZED USE

- Molnupiravir is not authorized for use in patients who are less than 18 years of age [see *Warnings and Precautions* (5.2)].
- Molnupiravir is not authorized for initiation of treatment in patients hospitalized due to COVID-19². Benefit of treatment with molnupiravir has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 [see *Dosing and Administration* (2.1)].
- Molnupiravir is not authorized for use for longer than 5 consecutive days.
- Molnupiravir is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Molnupiravir may only be prescribed for an individual patient by physicians, advanced practice registered nurses, and physician assistants that are licensed or authorized under state law to prescribe drugs in the therapeutic class to which molnupiravir belongs (i.e., anti-infectives).

Molnupiravir is not approved for any use, including for use for the treatment of COVID-19.

¹ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

² Should a patient require hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider’s discretion.

Prior to initiating treatment with molnupiravir, carefully consider the known and potential risks and benefits [see *Warnings and Precautions (5.1, 5.2)*, *Use in Specific Populations (8.1, 8.3)* and *Nonclinical Toxicology (13.1)*].

Molnupiravir is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of molnupiravir under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Justification for Emergency Use of Drugs During the COVID-19 Pandemic

There is currently an outbreak of Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2, a novel coronavirus. The Secretary of HHS has declared that:

- A public health emergency related to COVID-19 has existed since January 27, 2020.
- Circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic (March 27, 2020 declaration).

An EUA is a FDA authorization for the emergency use of an unapproved product or unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain circumstances including, but not limited to, when the Secretary of HHS declares that there is a public health emergency that affects the national security or the health and security of United States citizens living abroad, and that involves biological agent(s) or a disease or condition that may be attributable to such agent(s). Criteria for issuing an EUA include:

- The biological agent(s) can cause a serious or life-threatening disease or condition;
- Based on the totality of the available scientific evidence (including data from adequate and well-controlled clinical trials, if available), it is reasonable to believe that
 - the product may be effective in diagnosing, treating, or preventing the serious or life-threatening disease or condition; and
 - the known and potential benefits of the product - when used to diagnose, prevent, or treat such disease or condition - outweigh the known and potential risks of the product, taking into consideration the material threat posed by the biological agent(s);
- There is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the serious or life-threatening disease or condition.

Information Regarding Available Alternatives for the EUA Authorized Use

Other therapeutics are currently authorized for the same use as molnupiravir. For additional information on all products authorized for treatment or prevention of COVID-19, please see <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage for Emergency Use of Molnupiravir in Adult Patients

The dosage in adult patients is 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food [see *Clinical Pharmacology (12.3)*]. Take molnupiravir as soon as possible after a diagnosis of COVID-19 has been made, and within 5 days of symptom onset [see *Emergency Use Authorization (1)* and *Clinical Studies (14)*].

Completion of the full 5-day treatment course and continued isolation in accordance with public health recommendations are important to maximize viral clearance and minimize transmission of SARS-CoV-2 [see *Patient Counseling Information (17)*].

Molnupiravir is not authorized for use for longer than 5 consecutive days because the safety and efficacy have not been established.

If the patient misses a dose of molnupiravir within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. The patient should not double the dose to make up for a missed dose.

Should a patient require hospitalization after starting treatment with molnupiravir, the patient may complete the full 5 day treatment course per the healthcare provider's discretion.

2.2 Dosage Adjustments in Specific Populations

No dosage adjustment is recommended based on renal or hepatic impairment or in geriatric patients [see *Use in Specific Populations* (8.5, 8.6, 8.7)].

3 DOSAGE FORMS AND STRENGTHS

Capsules: 200 mg, Swedish Orange opaque size 0 capsules. The capsules have the corporate logo and "82" printed in white ink.

4 CONTRAINDICATIONS

No contraindications have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for molnupiravir. Serious and unexpected adverse events may occur that have not been previously reported with molnupiravir use.

5.1 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, molnupiravir is not recommended for use during pregnancy. When considering molnupiravir for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using molnupiravir during pregnancy to the pregnant individual. Molnupiravir is authorized to be prescribed to a pregnant individual only after the healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and the potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual.

Advise individuals of childbearing potential of the potential risk to a fetus and to use an effective method of contraception correctly and consistently, as applicable, during treatment with molnupiravir and for 4 days after the final dose [see *Use in Specific Populations* (8.1, 8.3 and *Nonclinical Toxicology* (13.1))].

Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated. Pregnancy status does not need to be confirmed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible. In all other patients, assess whether the patient is pregnant based on the first day of last menstrual period in individuals who have regular menstrual cycles, is using a reliable method of contraception correctly and consistently or have had a negative pregnancy test. A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of last menstrual period or is not using effective contraception correctly and consistently [see *Box*].

5.2 Bone and Cartilage Toxicity

Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth. Bone and cartilage toxicity was observed in rats after repeated dosing [see *Nonclinical Toxicity (13.2)*]. The safety and efficacy of molnupiravir have not been established in pediatric patients [see *Use in Specific Populations (8.4)*].

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Studies

The following adverse reactions have been observed in the clinical study of molnupiravir that supported the EUA. The adverse reaction rates observed in these clinical trials cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Additional adverse events associated with molnupiravir may become apparent with more widespread use.

Overall, more than 900 subjects have been exposed to molnupiravir 800 mg twice daily in clinical trials. The safety assessment of molnupiravir is primarily based on an analysis from subjects followed through Day 29 in the Phase 3 study in non-hospitalized subjects with COVID-19 (MOVE-OUT) [see *Clinical Studies (14)*].

The safety of molnupiravir was evaluated based on an analysis of a Phase 3 double-blind trial (MOVE-OUT) in which 1,411 non-hospitalized subjects with COVID-19 were randomized and treated with molnupiravir (N=710) or placebo (N=701) for up to 5 days. Adverse events were those reported while subjects were on study intervention or within 14 days of study intervention completion/discontinuation.

Discontinuation of study intervention due to an adverse event occurred in 1% of subjects receiving molnupiravir and 3% of subjects receiving placebo. Serious adverse events occurred in 7% of subjects receiving molnupiravir and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) subjects receiving molnupiravir and 12 (2%) of subjects receiving placebo.

The most common adverse reactions in the molnupiravir treatment group in MOVE-OUT are presented in Table 1, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 1% of Subjects Receiving Molnupiravir in MOVE-OUT*

	Molnupiravir N=710	Placebo N=701
Diarrhea	2%	2%
Nausea	1%	1%
Dizziness	1%	1%
*Frequencies of adverse reactions are based on all adverse events attributed to study intervention by the investigator.		

Laboratory Abnormalities

Selected Grade 3 and 4 laboratory abnormalities in chemistry (alanine aminotransferase, aspartate aminotransferase, creatinine, and lipase) and hematology (hemoglobin, platelets, and leukocytes) parameters all occurred at a rate of less than or equal to 2% and occurred at a similar rate across arms in MOVE-OUT.

6.4 Required Reporting for Serious Adverse Events and Medication Errors

The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to molnupiravir within 7 calendar days from the healthcare provider's awareness of the event, using

FDA Form 3500 (for information on how to access this form, see below). The FDA recommends that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Molnupiravir use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:
 - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
 - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:
Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA
Fax: 215-616-5677
E-mail: d poc.usa@msd.com

The prescribing healthcare provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors associated with molnupiravir.

Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

7 DRUG INTERACTIONS

No drug interactions have been identified based on the limited available data on the emergency use of molnupiravir authorized under this EUA. No clinical drug-drug interaction trials of molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, have been conducted [see *Clinical Pharmacology* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Surveillance Program

There is a pregnancy surveillance program that monitors pregnancy outcomes in individuals exposed to molnupiravir during pregnancy. The prescribing healthcare provider must document

that a pregnant individual was made aware of Merck Sharp & Dohme's pregnancy surveillance program at 1-877-888-4231 or pregnancyreporting.msd.com. If the pregnant individual agrees to participate in the pregnancy surveillance program and allows the prescribing healthcare provider to disclose patient specific information to Merck Sharp & Dohme, the prescribing healthcare provider must provide the patient's name and contact information to Merck Sharp & Dohme. Pregnant individuals exposed to molnupiravir can also report the exposure by contacting Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-877-888-4231 or pregnancyreporting.msd.com.

Risk Summary

Based on animal data, molnupiravir may cause fetal harm when administered to pregnant individuals. There are no available human data on the use of molnupiravir in pregnant individuals to evaluate the risk of major birth defects, miscarriage or adverse maternal or fetal outcomes; therefore, molnupiravir is not recommended during pregnancy [see *Box and Warnings and Precautions (5.1)*]. In an animal reproduction study, oral administration of molnupiravir to pregnant rats during the period of organogenesis resulted in embryofetal lethality and teratogenicity at 8 times the human NHC (N4-hydroxycytidine) exposures at the recommended human dose (RHD) and reduced fetal growth at ≥ 3 times the human NHC exposure at the RHD. Oral administration of molnupiravir to pregnant rabbits during the period of organogenesis resulted in reduced fetal body weights at 18 times the human NHC exposure at the RHD (see *Data*). When considering molnupiravir for a pregnant individual, the prescribing healthcare provider must communicate the known and potential benefits and the potential risks of using molnupiravir during pregnancy to the pregnant individual. Molnupiravir may only be prescribed to a pregnant individual after the prescribing healthcare provider has determined that the benefits would outweigh the risks for that individual patient. If the decision is made to use molnupiravir during pregnancy, the prescribing healthcare provider must document that the known and potential benefits and potential risks of using molnupiravir during pregnancy were communicated to the pregnant individual [see *Box*]. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy (see *Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Animal Data

In an embryofetal development (EFD) study in rats, molnupiravir was administered orally to pregnant rats at 0, 100, 250, or 500 mg/kg/day from gestation days (GDs) 6 to 17. Molnupiravir was also administered orally to pregnant rats at up to 1,000 mg/kg/day from GDs 6 to 17 in a preliminary EFD study. Developmental toxicities included post-implantation losses, malformations of the eye, kidney, and axial skeleton, and rib variations at 1,000 mg/kg/day (8 times the human NHC exposure at the RHD) and decreased fetal body weights and delayed ossification at ≥ 500 mg/kg/day (3 times the human NHC exposure at the RHD). There were no developmental toxicities at ≤ 250 mg/kg/day (less than the human NHC exposure at the RHD). Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of two of sixteen animals at 1,000 mg/kg/day, and decreased body weight gain at 500 mg/kg/day.

In an EFD study in rabbits, molnupiravir was administered orally to pregnant rabbits at 0, 125, 400, or 750 mg/kg/day from GDs 7 to 19. Developmental toxicity was limited to reduced fetal

body weights at 750 mg/kg/day (18 times the human NHC exposures at the RHD). There was no developmental toxicity at ≤ 400 mg/kg/day (7 times the human NHC exposures at the RHD). Maternal toxicities included reduced food consumption and body weight gains, and abnormal fecal output at 750 mg/kg/day.

In a pre- and post-natal developmental study, molnupiravir was administered orally to female rats at doses up to 500 mg/kg/day (similar to the human NHC exposure at the RHD) from GD6 through lactation day 20. No effects were observed in offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of molnupiravir or its metabolites in human milk. NHC was detected in the plasma of nursing pups from lactating rats administered molnupiravir (see *Data*). It is unknown whether molnupiravir has an effect on the breastfed infant or effects on milk production.

Based on the potential for adverse reactions in the infant from molnupiravir, breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the final dose. A lactating individual may consider interrupting breastfeeding and may consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir [see *Warnings and Precautions (5.1, 5.2)*].

Data

When molnupiravir was administered to lactating rats at ≥ 250 mg/kg/day in the pre- and post-natal development study, NHC was detected in plasma of nursing pups.

8.3 Females and Males of Reproductive Potential

Based on animal studies, molnupiravir may cause fetal harm when administered to a pregnant individual.

Pregnancy Testing

Prior to initiating treatment with molnupiravir, assess whether an individual of childbearing potential is pregnant or not, if clinically indicated [see *Warnings and Precautions (5.1)*].

Contraception

Females

Advise individuals of childbearing potential to use a reliable method of contraception correctly and consistently, as applicable for the duration of treatment and for 4 days after the last dose of molnupiravir [see *Warnings and Precautions (5.1)*].

Males

While the risk is regarded as low, nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir. The risk beyond three months after the last dose of molnupiravir is unknown. Studies to understand the risk beyond three months are ongoing.

Molnupiravir was equivocal (neither clearly positive nor negative) in one *in vivo* mutagenicity assay of reticulocytes and RBCs which are used to reflect prior effects on hematopoietic stem cells in bone marrow. Molnupiravir was not mutagenic when assessed in a second *in vivo* assay of liver (somatic cells) and bone marrow (somatic cells and stem cells) from transgenic rats administered molnupiravir for 28 days. In contrast to somatic cells, germ cells (eggs and sperm) pass genetic information from generation to generation. A planned study of male testicular germ cells from transgenic rats will assess the potential for molnupiravir to affect offspring of treated males [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Molnupiravir is not authorized for use in patients less than 18 years of age. Bone and cartilage toxicity were observed in a 3-month, repeat-dose toxicology study in rats. The safety and efficacy of molnupiravir have not been established in pediatric patients [see *Warnings and Precautions (5.2) and Nonclinical Toxicology (13.2)*].

8.5 Geriatric Use

In MOVE-OUT, there was no difference in safety and tolerability between patients ≥ 65 years of age and younger patients who were treated with molnupiravir. No dosage adjustment is recommended based on age. The PK of NHC was similar in geriatric patients compared to younger patients [see *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

No dosage adjustment in patients with any degree of renal impairment is recommended. Renal clearance is not a meaningful route of elimination for NHC. Mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. While the PK of NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m² or on dialysis, severe renal impairment, and end-stage renal disease (ESRD) are not expected to have a significant effect on NHC exposure [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

No dosage adjustment in patients with hepatic impairment is recommended. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination therefore, hepatic impairment is unlikely to affect NHC exposure [see *Clinical Pharmacology (12.3)*].

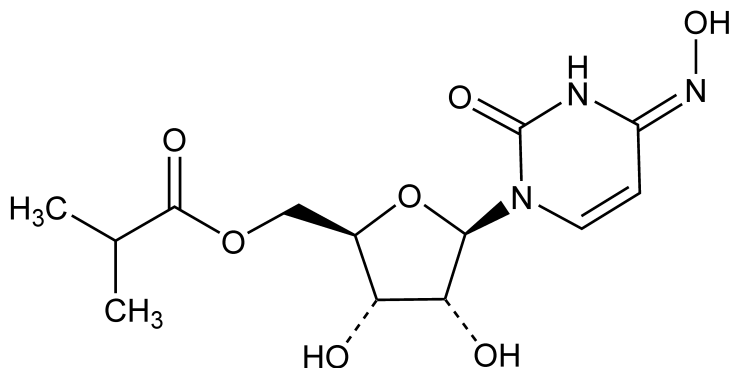
10 OVERDOSAGE

There is no human experience of overdose with molnupiravir. Treatment of overdose with molnupiravir should consist of general supportive measures including the monitoring of the clinical status of the patient. Hemodialysis is not expected to result in effective elimination of NHC.

11 DESCRIPTION

Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis and is the 5'-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC).

The chemical name for molnupiravir is {(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. It has an empirical formula of C₁₃H₁₉N₃O₇ and its molecular weight is 329.31 g/mol. Its structural formula is:



Molnupiravir is a white to off-white powder that is soluble in water.

Each molnupiravir capsule, for oral use, contains 200 mg of molnupiravir and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Molnupiravir is a prodrug with antiviral activity against SARS-CoV-2. It is metabolized to the cytidine nucleoside analogue, NHC which distributes into cells where NHC is phosphorylated to form the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA by the viral RNA polymerase (nsp12) results in an accumulation of errors in the viral genome leading to inhibition of replication. The mechanism of action (known as viral error catastrophe or viral lethal mutagenesis) is supported by biochemical and cell culture data, studies of SARS-CoV-2 infection in animal models, and analyses of SARS-CoV-2 genome sequences in human subjects treated with molnupiravir.

12.2 Pharmacodynamics

The relationship between NHC and intracellular NHC-TP with antiviral efficacy has not been evaluated clinically.

12.3 Pharmacokinetics

Molnupiravir is a 5'-isobutyrate prodrug of NHC that is hydrolyzed during or after absorption. NHC, the primary circulating analyte, is taken up by cells and anabolized to NHC-TP. NHC is eliminated by metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism. NHC pharmacokinetics are shown in Table 2.

Table 2: Pharmacokinetics of NHC After Multiple Oral Administration of 800 mg Molnupiravir Every 12 Hours

	NHC Geometric Mean (%CV)
Pharmacokinetics in Patients	
AUC _{0-12hr} (ng*hr/mL) [*]	8260 (41.0)
C _{max} (ng/mL) [*]	2330 (36.9)
C _{12hr} (ng/mL) [*]	31.1 (124)
Pharmacokinetics in Healthy Subjects	
AUC _{0-12hr} (ng*hr/mL)	8330 (17.9)
C _{max} (ng/mL)	2970 (16.8)
C _{12hr} (ng/mL)	16.7 (42.8)
AUC Accumulation Ratio	1.09 (11.8)
Absorption	
T _{max} (hr) [†]	1.50 [1.00 – 2.02]
Effect of Food	35% reduction in C _{max} , no effect on AUC
Distribution	
Plasma Protein Binding (<i>in vitro</i>)	0%
Apparent Volume of Distribution (L) [*]	142
Elimination	
Effective t _{1/2} (hr)	3.3
Apparent Clearance (L/hr) [*]	76.9
Fraction of dose excreted in urine over the time interval of 0-12 hours	3% (81.6%)

Values were obtained from a Phase 1 study of healthy subjects, unless otherwise indicated.

^{*}Values were obtained from population PK analysis.

†Median [min - max]

Specific Populations

Population PK analysis results indicated that age, sex, race, ethnicity, or disease severity do not meaningfully influence the PK of NHC.

Pediatric Patients

Molnupiravir has not been studied in pediatric patients.

Patients with Renal Impairment

Renal clearance is not a meaningful route of elimination for NHC. In a population PK analysis, mild or moderate renal impairment did not have a meaningful impact on the PK of NHC. The PK of molnupiravir and NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m² or on dialysis.

Patients with Hepatic Impairment

The PK of molnupiravir and NHC has not been evaluated in patients with moderate and severe hepatic impairment. Preclinical data indicate that hepatic elimination is not expected to be a major route of NHC elimination; therefore, hepatic impairment is unlikely to affect NHC exposure.

Drug Interaction Studies

In vitro study results indicated that molnupiravir and NHC are not substrates of CYP enzymes or human P-gp and BCRP transporters. *In vitro* study results also indicated that molnupiravir and NHC are not inhibitors of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 or inhibitors of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2K, MRP2, MDR1 and BCRP or inducers of CYP1A2, 2B6, and 3A4. The interaction between molnupiravir with concomitant medications, including other treatments for mild-to-moderate COVID-19, has not been evaluated.

12.4 Microbiology

Antiviral Activity

NHC, the nucleoside analogue metabolite of molnupiravir, was active in cell culture assays against SARS-CoV-2 with 50% effective concentrations (EC₅₀ values) ranging between 0.67 to 2.66 µM in A-549 cells and 0.32 to 2.03 µM in Vero E6 cells. NHC had similar activity against SARS-CoV-2 variants Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2) with EC₅₀ values of 1.59, 1.77 and 1.32 and 1.68 µM, respectively. NHC had non-antagonistic antiviral activity with remdesivir against SARS-CoV-2 in cell culture.

Resistance

No amino acid substitutions in SARS-CoV-2 associated with resistance to NHC have been identified in Phase 2 clinical trials evaluating molnupiravir for the treatment of COVID-19. Studies to evaluate selection of resistance to NHC with SARS-CoV-2 in cell culture have not been completed. Resistance selection studies have been conducted with other coronaviruses (MHV and MERS-CoV) and showed a low likelihood of resistance development to NHC. Following 30 passages in cell culture, only a 2-fold decrease in susceptibility was observed and no NHC resistance-associated amino acid substitutions were identified. NHC retained activity in cell culture against virus with polymerase (nsp 12) substitutions (e.g., F480L, V557L and E802D) associated with decreased remdesivir sensitivity, indicating a lack of cross-resistance.

In clinical trials, encoded amino acid changes (substitutions, deletions or insertions) were more likely to be detected in viral sequences in subjects treated with molnupiravir compared to placebo. In a small number of subjects amino acid changes in the spike protein occurred at positions targeted by monoclonal antibodies and vaccines. The clinical and public health significance of these changes are unknown.

Activity against SARS-CoV-2 in animal models

The antiviral activity of molnupiravir has been demonstrated in mouse, hamster, and ferret models of SARS-CoV-2 infection when dosing was administered prior to or within 1-2 days after viral challenge. In SARS-CoV-2 infected ferrets, molnupiravir significantly reduced SARS-CoV-2 viral titers in the upper respiratory tract and completely inhibited viral spread to untreated contact animals. In SARS-CoV-2 infected Syrian hamsters, molnupiravir reduced viral RNA and infectious virus titers in the lungs of animals. Histopathological analysis of lung tissue harvested after infection showed significantly reduced SARS-CoV-2 viral antigen levels and a lower abundance of pulmonary lesions in molnupiravir-treated animals compared with controls.

In Vitro Cytotoxicity

NHC, the nucleoside analogue metabolite of molnupiravir, had variable cytotoxicity against different mammalian cell types with CC₅₀ values ranging from 7.5 µM (human lymphoid CEM cell line) to >100 µM, in 3-day exposure assays. Molnupiravir inhibited the proliferation of human bone marrow progenitor cells with CC₅₀ values of 24.9 µM and 7.7 µM for erythroid and myeloid progenitor proliferation, respectively, in 14-day colony formation assays.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A mouse carcinogenicity study with molnupiravir is ongoing.

Mutagenesis

Molnupiravir and NHC were positive in the *in vitro* bacterial reverse mutation assay (Ames assay) with and without metabolic activation. Molnupiravir was studied in two *in vivo* rodent mutagenicity models. The *in vivo* Pig-a mutagenicity assay gave equivocal results. Molnupiravir was negative in the *in vivo* Big Blue® (cII Locus) transgenic rodent mutagenicity assay. Molnupiravir was negative for induction of chromosomal damage in *in vitro* micronucleus (with and without metabolic activation) and *in vivo* rat micronucleus assays. To assess effects on germ cells, a transgenic rodent male germ cell mutagenicity assay is planned.

Based on the totality of the available genotoxicity data and the duration of treatment (5 days), molnupiravir is low risk for genotoxicity.

Impairment of Fertility

There were no effects on fertility, mating performance or early embryonic development when molnupiravir was administered to female or male rats at NHC exposures approximately 2 and 6 times, respectively, the human NHC exposure at the RHD.

13.2 Animal Toxicology and/or Pharmacology

Bone and cartilage toxicity changes resulting in impaired transformation of growth cartilage into new bone were observed in the femur and tibia of rats in a 3-month toxicity study at ≥ 500 mg/kg/day (5 times the human NHC exposure at the RHD). There was no bone or cartilage toxicity in a 1-month toxicity study in rats up to 500 mg/kg/day (4 and 8 times the human NHC exposure at the RHD in females and males, respectively), in dogs dosed for 14 days up to 50 mg/kg/day (similar to the human NHC exposure at the RHD), or in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD).

Growth cartilage is not present in mature skeletons, therefore the bone and cartilage findings are not relevant for adult humans but may be relevant for pediatric patients [see *Warnings and Precautions (5.2) and Use in Specific Populations (8.4)*].

Reversible, dose-related bone marrow toxicity affecting all hematopoietic cell lines was observed in dogs at ≥17 mg/kg/day (less than the human NHC exposure at the RHD). Mild decreases in peripheral blood cell and platelet counts were seen after 7 days of molnupiravir treatment progressing to more severe hematological changes after 14 days of treatment. Neither bone

marrow nor hematological toxicity was observed in a 1-month toxicity study in mice up to 2,000 mg/kg/day (19 times the human NHC exposure at the RHD) and a 3-month toxicity study in rats up to 1,000 mg/kg/day (9 and 15 times the human NHC exposure at the RHD in females and males, respectively).

14 CLINICAL STUDIES

Clinical data supporting this EUA are based on data from 1,433 randomized subjects in the Phase 3 MOVE-OUT trial (NCT04575597). MOVE-OUT is a randomized, placebo-controlled, double-blind clinical trial studying molnupiravir for the treatment of non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Eligible subjects were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI \geq 30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. The study included symptomatic subjects not vaccinated against SARS-CoV-2 and who had laboratory confirmed SARS-CoV-2 infection and symptom onset within 5 days of randomization. Subjects were randomized 1:1 to receive 800 mg of molnupiravir or placebo orally twice daily for 5 days.

At baseline, in all randomized subjects, the median age was 43 years (range:18 to 90); 17% of subjects were over 60 years of age and 3% were 75 years of age or older; 49% of subjects were male; 57% were White, 5% Black or African American, 3% Asian, 50% Hispanic or Latino. The majority of subjects were enrolled from sites in Latin America (46%) and Europe (33%); 12% were enrolled in Africa, 6% were enrolled in North America and 3% were enrolled in Asia. Forty-eight percent of subjects received molnupiravir or placebo within 3 days of COVID-19 symptom onset. The most common risk factors were obesity (74%), over 60 years of age (17%), and diabetes (16%). Among 792 subjects (55% of total randomized population) with available baseline SARS-CoV-2 variant/clade identification results, 58% were infected with Delta (B.1.617.2 and AY lineages), 20% were infected with Mu (B.1.621), 11% were infected with Gamma (P.1), and the remainder were infected with other variants/clades. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

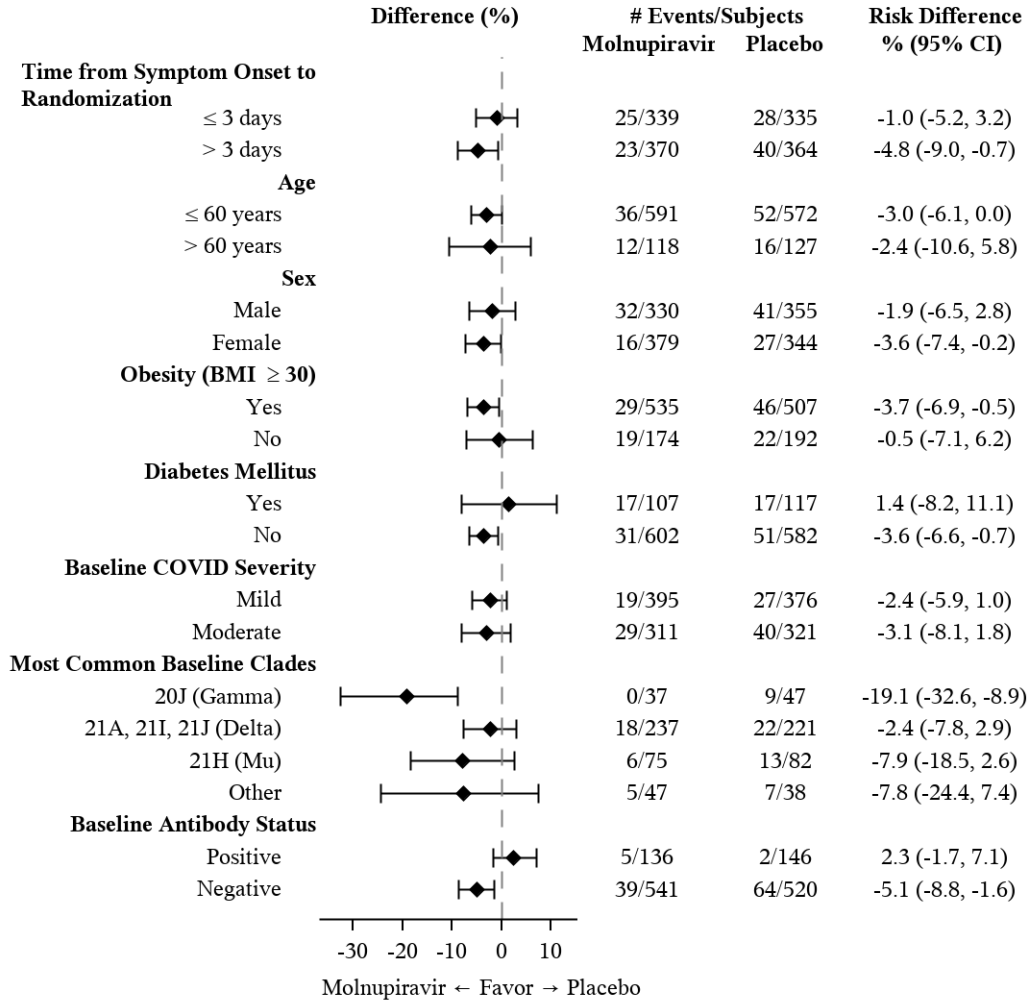
Table 3 provides the results of the primary endpoint (the percentage of subjects who were hospitalized or died through Day 29 due to any cause). The efficacy results are based on unvaccinated adults who were 18 years of age and older and had one or more pre-defined risk factors for disease progression: over 60 years of age, diabetes, obesity (BMI \geq 30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer. Please refer to Figure 1 for results by certain subgroups. These subgroup analyses are considered exploratory. Data are not available in certain subgroups of subjects who are at high risk for progression to severe COVID-19 as defined by CDC.

Table 3. Efficacy Results in Non-Hospitalized Adults with COVID-19*

Molnupiravir (N=709)	Placebo (N=699)	Adjusted Risk Difference % (95% CI)
n (%)	n (%)	
All-cause hospitalization \geq24 hours for acute care or death through Day 29		
48 (6.8%)	68 (9.7%)	-3.0% (-5.9%, -0.1%)
All-cause mortality through Day 29		
1 (0.1%)	9 (1.3%)	
*The determination of primary efficacy was based on a planned interim analysis of 762 subjects. At the interim analysis, 7.3% of patients who received molnupiravir were either hospitalized or died through Day 29 (28/385), compared with 14.1% of placebo-treated patients (53/377). The adjusted risk difference was -6.8% with a 95% CI of (-11.3%, -2.4%) and 2-sided p-value = 0.0024.		

Adjusted relative risk reduction of molnupiravir compared to placebo for all randomized subjects was 30% (95% CI: 1%, 51%).
 Analyses are adjusted by the stratification factor of time of COVID-19 symptom onset (≤ 3 days vs. >3 [4-5] days).

Figure 1. Subgroup Efficacy Results in Non-Hospitalized Adults with COVID-19 - All-Randomized Subjects



The corresponding confidence interval is based on Miettinen & Nurminen method.
 The modified intent-to-treat population is the efficacy analysis population.
 Baseline serum samples were evaluated with the Roche Elecsys anti-N assay to test for the presence of antibodies (IgM, IgG and IgA) against the SARS-CoV-2 nucleocapsid protein.
 The findings of these subgroup analyses are considered exploratory.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Molnupiravir capsules are supplied as follows:

Contents	Description	How Supplied	NDC
200 mg molnupiravir	Swedish Orange opaque capsules with corporate logo and "82" printed in white ink	40 count bottles	NDC-0006-5055-06 NDC-0006-5055-07

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Storage and Handling

Store molnupiravir capsules at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see *USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION

As a prescribing healthcare practitioner, you must communicate to the patient and/or caregiver information consistent with the “FACT SHEET FOR PATIENTS AND CAREGIVERS” and document that information was provided. A copy of this Fact Sheet should be provided to the patient and/or caregiver prior to receiving molnupiravir [see *Box*].

Risk of Fetal Toxicity

Advise patients that molnupiravir is not recommended for use in pregnancy because it may cause fetal harm. Advise individuals of childbearing potential to inform their healthcare provider of a known or suspected pregnancy [see *Box, Warnings and Precautions (5.1) and Use in Specific Populations (8.1)*].

Advise individuals of childbearing potential to use effective contraception correctly and consistently while taking molnupiravir and for 4 days after the last dose.

While the risk is regarded as low, nonclinical studies to fully assess the potential for molnupiravir to affect offspring of treated males have not been completed. Advise sexually active individuals with partners of childbearing potential to use a reliable method of contraception consistently and correctly while taking molnupiravir and for at least 3 months after the last dose of molnupiravir. The risk beyond 3 months after the last dose of molnupiravir is unknown. Studies to understand the risk beyond three months are ongoing [see *Use in Specific Populations (8.3)*].

Risk of Bone and Cartilage Toxicity

Molnupiravir is not authorized for use in patients less than 18 year of age as it may affect bone growth and cartilage formation [see *Warnings and Precautions (5.2) and Use in Specific Populations (8.4)*].

Pregnancy Surveillance Program

There is a pregnancy surveillance program that monitors pregnancy outcomes in individuals exposed to molnupiravir during pregnancy. Encourage participation and advise patients about how they may enroll in the pregnancy surveillance program. Advise patients who have taken molnupiravir during pregnancy to report their pregnancy to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA at 1-877-888-4231 or pregnancyreporting.msd.com [see *Use in Specific Populations (8.1)*].

Lactation

Breastfeeding is not recommended while taking molnupiravir and for 4 days after the last dose of molnupiravir. Advise lactating individuals to consider interrupting breastfeeding and to consider pumping and discarding breast milk during treatment and for 4 days after the last dose of molnupiravir [see *Use in Specific Populations (8.2)*].

Administration Instructions

Inform patients to take molnupiravir with or without food. Advise patients to swallow molnupiravir capsules whole, and to not open, break, or crush the capsules. Instruct patients that if they miss a dose of molnupiravir and it is within 10 hours of the time it is usually taken, the patient should take it as soon as possible and resume the normal dosing schedule. If the patient misses a dose by more than 10 hours, the patient should not take the missed dose and instead take the next dose at the regularly scheduled time. Advise the patient to not double the dose to make up for a missed dose [see *Dosage and Administration (2.2)*].

Alert the patient of the importance of completing the full 5-day treatment course and to continuing isolation in accordance with public health recommendations to maximize viral clearance and minimize transmission of SARS-CoV-2 [see *Dosage and Administration (2.2)*].

18 MANUFACTURER INFORMATION

For additional information visit: www.molnupiravir.com

If you have questions, please contact
1-800-672-6372

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

For patent information: www.msd.com/research/patent

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Fact Sheet for Patients And Caregivers
Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019
(COVID-19)

What is the most important information I should know about molnupiravir?

Molnupiravir may cause serious side effects, including:

- **Molnupiravir may cause harm to your unborn baby. It is not known if molnupiravir will harm your baby if you take molnupiravir during pregnancy.**
 - Molnupiravir is not recommended for use in pregnancy.
 - Molnupiravir has not been studied in pregnancy. Molnupiravir was studied in pregnant animals only. When molnupiravir was given to pregnant animals, molnupiravir caused harm to their unborn babies.
 - You and your healthcare provider may decide that you should take molnupiravir during pregnancy if there are no other COVID-19 treatment options authorized by the FDA that are accessible or clinically appropriate for you.
 - If you and your healthcare provider decide that you should take molnupiravir during pregnancy, you and your healthcare provider should discuss the known and potential benefits and the potential risks of taking molnupiravir during pregnancy.

For individuals who are able to become pregnant:

- You should use a reliable method of birth control (contraception) consistently and correctly during treatment with molnupiravir and for 4 days after the last dose of molnupiravir. Talk to your healthcare provider about reliable birth control methods.
- Before starting treatment with molnupiravir your healthcare provider may do a pregnancy test to see if you are pregnant before starting treatment with molnupiravir.
- Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with molnupiravir.

Pregnancy Surveillance Program:

- There is a pregnancy surveillance program for individuals who take molnupiravir during pregnancy. The purpose of this program is to collect information about the health of you and your baby. Talk to your healthcare provider about how to take part in this program.
- If you take molnupiravir during pregnancy and you agree to participate in the pregnancy surveillance program and allow your healthcare provider to share your information with Merck Sharp & Dohme, then your healthcare provider will report your use of molnupiravir during pregnancy to Merck Sharp & Dohme Corp. by calling 1-877-888-4231 or [pregnancyreporting.msd.com](https://www.msd.com/pregnancyreporting).

For individuals who are sexually active with partners who are able to become pregnant:

- It is not known if molnupiravir can affect sperm. While the risk is regarded as low, animal studies to fully assess the potential for molnupiravir to affect the babies of males treated with molnupiravir have not been completed. A reliable method of birth control (contraception) should be used consistently and correctly during treatment with molnupiravir and for at least 3 months after the last dose. The risk to sperm beyond 3 months is not known. Studies to understand the risk to sperm beyond 3 months are ongoing. Talk to your healthcare provider

about reliable birth control methods. Talk to your healthcare provider if you have questions or concerns about how molnupiravir may affect sperm.

You are being given this fact sheet because your healthcare provider believes it is necessary to provide you with molnupiravir for the treatment of adults with mild-to-moderate coronavirus disease 2019 (COVID-19) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 including hospitalization or death, and for whom other COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to make molnupiravir available during the COVID-19 pandemic (for more details about an EUA please see “**What is an Emergency Use Authorization?**” at the end of this document). Molnupiravir is not an FDA-approved medicine in the United States. Read this Fact Sheet for information about molnupiravir. Talk to your healthcare provider about your options if you have any questions. It is your choice to take molnupiravir.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. You can get COVID-19 through close contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild-to-severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of your other medical conditions to become worse. Older people and people of all ages with severe, long lasting (chronic) medical conditions like heart disease, lung disease and diabetes, for example seem to be at higher risk of being hospitalized for COVID-19.

What is molnupiravir?

Molnupiravir is an investigational medicine used to treat mild-to-moderate COVID-19 in adults:

- with positive results of direct SARS-CoV-2 viral testing, and
- who are at high risk for progressing to severe COVID-19 including hospitalization or death, and for whom other COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.

The FDA has authorized the emergency use of molnupiravir for the treatment of mild-to-moderate COVID-19 in adults under an EUA. For more information on EUA, see the “**What is an Emergency Use Authorization (EUA)?**” section at the end of this Fact Sheet.

Molnupiravir is not authorized:

- for use in people less than 18 years of age.
- for prevention of COVID-19.
- for people needing hospitalization for COVID-19.
- for use for longer than 5 consecutive days.

What should I tell my healthcare provider before I take molnupiravir?

Tell your healthcare provider if you:

- Have any allergies
- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products).

How do I take molnupiravir?

- Take molnupiravir exactly as your healthcare provider tells you to take it.
- Take 4 capsules of molnupiravir every 12 hours (for example, at 8 am and at 8 pm)
- **Take molnupiravir for 5 days.** It is important that you complete the full 5 days of treatment with molnupiravir. Do not stop taking molnupiravir before you complete the full 5 days of treatment, even if you feel better.
- Take molnupiravir with or without food.
- You should stay in isolation for as long as your healthcare provider tells you to. Talk to your healthcare provider if you are not sure about how to properly isolate while you have COVID-19.
- Swallow molnupiravir capsules whole. Do not open, break, or crush the capsules. If you cannot swallow capsules whole, tell your healthcare provider.
- **What to do if you miss a dose:**
 - If it has been **less than 10 hours** since the missed dose, take it as soon as you remember
 - If it has been **more than 10 hours** since the missed dose, skip the missed dose and take your dose at the next scheduled time.
- Do not double the dose of molnupiravir to make up for a missed dose.

What are the important possible side effects of molnupiravir?

Possible side effects of molnupiravir are:

- See, “**What is the most important information I should know about molnupiravir?**”
- diarrhea
- nausea
- dizziness

These are not all the possible side effects of molnupiravir. Not many people have taken molnupiravir. Serious and unexpected side effects may happen. This medicine is still being studied, so it is possible that all of the risks are not known at this time.

What other treatment choices are there?

Like molnupiravir, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization> for more information.

It is your choice to be treated or not to be treated with molnupiravir. Should you decide not to take it, it will not change your standard medical care.

What if I am breastfeeding?

Breastfeeding is not recommended during treatment with molnupiravir and for 4 days after the last dose of molnupiravir. If you are breastfeeding or plan to breastfeed, talk to your healthcare provider about your options and specific situation before taking molnupiravir.

How do I report side effects with molnupiravir?

Contact your healthcare provider if you have any side effects that bother you or do not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call **1-800-FDA-1088** (1-800-332-1088).

How should I store molnupiravir?

- Store molnupiravir capsules at room temperature between 68°F to 77°F (20°C to 25°C).
- **Keep molnupiravir and all medicines out of the reach of children and pets.**

How can I learn more about COVID-19?

- Ask your healthcare provider.
- Visit www.cdc.gov/COVID19
- Contact your local or state public health department.
- Call Merck Sharp & Dohme at 1-800-672-6372 (toll free in the U.S.)
- Visit www.molnupiravir.com

What Is an Emergency Use Authorization (EUA)?

The United States FDA has made molnupiravir available under an emergency access mechanism called an Emergency Use Authorization (EUA) The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify emergency use of drugs and biological products during the COVID-19 pandemic.

Molnupiravir for the treatment of mild-to-moderate 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 authorized by FDA are not accessible or clinically appropriate, has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well-controlled clinical trials, if available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of patients during the COVID-19 pandemic. The EUA for molnupiravir is in effect for the duration of the COVID-19 declaration justifying emergency use of molnupiravir, unless terminated or revoked (after which molnupiravir may no longer be used under the EUA).

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

For patent information: www.msd.com/research/patent

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/s/

DAVID E ARAOJO
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KIMBERLY A STRUBLE
12/23/2021 07:17:04 AM

DEBRA B BIRNKRANT
12/23/2021 07:27:18 AM

JOHN J FARLEY
12/23/2021 08:15:19 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: Molnupiravir
Sponsor: Merck Sharp & Dohme
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 authorized by FDA are not accessible or clinically appropriate.

This addendum is for corrections to the summary EUA review for molnupiravir for the treatment of mild-to-moderate COVID-19 dated December 23, 2021.

The corrections are as follows:

On Page 1, “Senior” should be added prior to “Director” for Dr. Kumar’s title on page 1.

On page 73, “mild” should be changed to “milk.”

On pages 69 and 94, the pharmacokinetic/distribution study in rats should be changed from “ongoing” to “planned.” The study is planned to be initiated in mid-January 2022.

On page 98, “pediatrics” should be removed from the Supply Information section as molnupiravir is not authorized for use in pediatric patients.

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 or for Patients and Caregivers.

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/s/

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