U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Addendum to FDA Briefing Document

Antimicrobial Drugs Advisory Committee Meeting

November 30, 2021

On October 8, 2021, the sponsor (Merck & Co., Inc) submitted a request for Emergency Use Authorization for molnupiravir (MOV) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, based on a pre-specified P002 Part 2, interim analysis when approximately 50% of participants enrolled and completed the trial through Day 29. At the planned interim analysis (N=775 for efficacy and N=765 for safety), the external data monitoring committee recommended that due to efficacy on the primary endpoint of reducing hospitalization ≥24 hours for acute care of illness or death due to any cause by Day 29, the study met the criteria for stopping enrollment. The trial stopped enrollment, and all the randomized participants (N=1433) will continue to be followed until their Month 7 visit (end of study) or early withdrawal.

On November 22, 2021 the Agency became aware of the topline safety and efficacy results from all 1433 randomized participants (full population) through Day 29. Please refer to the sponsor's addendum for the updated efficacy and safety analyses. A few key updates include the following:

The number of participants who received MOV 800 mg Q12h for five days in Part 2 of P002 increased from 386 participants (interim population) to 710 participants (full population), bringing the total molnupiravir 800 mg safety database to 917 participants.

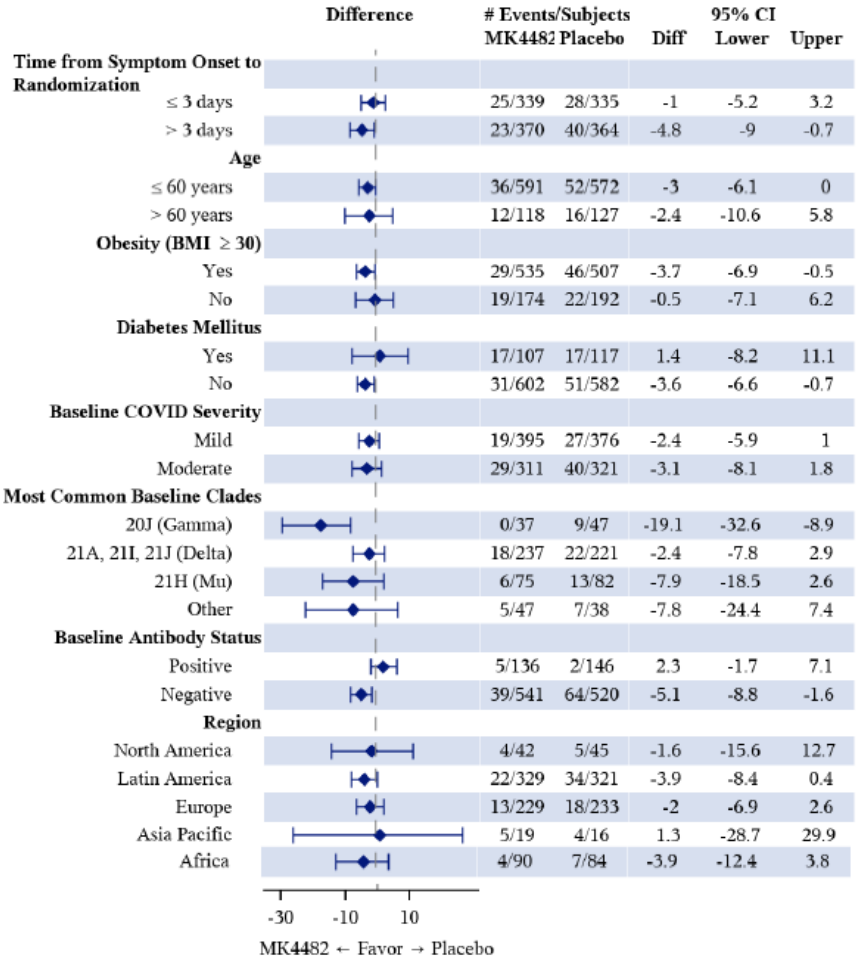
In the analysis submitted with the EUA request (interim population), all cause hospitalization or death through Day 29 was 7.3% (28/385) and 14.1% (53/377) for the MOV and placebo groups, respectively. The risk difference (MOV-Placebo) is -6.8 (95% CI: -11.3, -2.4) based on the Miettinen and Nurminen method stratified by time from COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).

In the updated analysis (full population), all cause hospitalization or death through Day 29 was 6.8% (48/709) and 9.7% (68/699) for the MOV and placebo groups, respectively. For the full population, the risk difference (MOV – Placebo) is -3.0% (95% CI: -5.9%, -0.1%) based on the Miettinen and Nurminen method stratified by time from COVID-19 symptom onset (≤3 days vs. >3 [4-5] days). The risk difference is the pre-specified primary analysis method. Additionally,

the relative risk reduction of MOV compared to placebo was 30% (95% CI: 1%, 51%) based on the Cochran-Mantel-Haenszel method stratified by time from COVID-19 symptom onset (≤3 days versus >3 [4 to 5] days). The incidence of hospitalization or death through Day 29 by subgroup for the full population is shown in Figure 1 (source, sponsor's analyses).

Figure 1

Incidence of Hospitalization or Death Through Day 29 by Subgroup (Protocol 002 – Full Population)



	# Events/Subjects MK4482	Placebo	95% CI Diff	Lower	Upper
Time from Symptom Onset to Randomization					
≤ 3 days	25/339	28/335	-1	-5.2	3.2
> 3 days	23/370	40/364	-4.8	-9	-0.7
Age					
≤ 60 years	36/591	52/572	-3	-6.1	0
> 60 years	12/118	16/127	-2.4	-10.6	5.8
Obesity (BMI ≥ 30)					
Yes	29/535	46/507	-3.7	-6.9	-0.5
No	19/174	22/192	-0.5	-7.1	6.2
Diabetes Mellitus					
Yes	17/107	17/117	1.4	-8.2	11.1
No	31/602	51/582	-3.6	-6.6	-0.7
Baseline COVID Severity					
Mild	19/395	27/376	-2.4	-5.9	1
Moderate	29/311	40/321	-3.1	-8.1	1.8
Most Common Baseline Clades					
20J (Gamma)	0/37	9/47	-19.1	-32.6	-8.9
21A, 21I, 21J (Delta)	18/237	22/221	-2.4	-7.8	2.9
21H (Mu)	6/75	13/82	-7.9	-18.5	2.6
Other	5/47	7/38	-7.8	-24.4	7.4
Baseline Antibody Status					
Positive	5/136	2/146	2.3	-1.7	7.1
Negative	39/541	64/520	-5.1	-8.8	-1.6
Region					
North America	4/42	5/45	-1.6	-15.6	12.7
Latin America	22/329	34/321	-3.9	-8.4	0.4
Europe	13/229	18/233	-2	-6.9	2.6
Asia Pacific	5/19	4/16	1.3	-28.7	29.9
Africa	4/90	7/84	-3.9	-12.4	3.8

The Agency continues to evaluate the known and potential benefits and risks of MOV considering the results from all randomized participants. During the meeting, the Agency will provide additional key safety and efficacy results based on all 1433 randomized participants (full population). The review issues and benefit/risk assessments may therefore differ from the original assessments provided in the briefing document which was based on the interim analysis.

Additionally, we are providing information from the November 4, 2019 FDA Genetic Toxicology Workshop: How Many Doses of an DNA Reactive (Ames-positive) Drug can be

Safely Administered to Healthy Subjects? The full transcript of the 2019 FDA workshop and other related workshop materials are available to the public at this link: https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/fda-genetic-toxicology-workshop-how-many-doses-dna-reactive-ames-positive-drug-can-be-safely#event-information.