Center for Drug Evaluation and Research

Antimicrobial Drugs Advisory Committee Meeting Briefing Document

Addendum

Molnupiravir

Oral Treatment of COVID-19

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ADVISORY COMMITTEE BRIEFING MATERIALS:
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1 PROTOCOL 002

Protocol 002 is a randomized, placebo-controlled, double-blind clinical trial studying molnupiravir for the treatment of non-hospitalized participants with mild to moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization. Participants were randomized 1:1 to receive 800 mg of molnupiravir or placebo orally twice daily for 5 days.

At the planned interim analysis, clinical data were available for 775 randomized participants. Molnupiravir reduced the risk of hospitalization or death by approximately 50%; 7.3% of participants who received molnupiravir were either hospitalized or died through Day 29 following randomization (28/385), compared with 14.1% of placebo-treated participants (53/377); p=0.0012. Through Day 29, no deaths were reported in participants who received molnupiravir, as compared to 8 deaths in participants who received placebo. Molnupiravir was generally well-tolerated with the rates of serious adverse events (SAEs), fatal AEs, and AEs leading to discontinuation all higher in the placebo arm than in the in molnupiravir arm. None of the SAEs was considered drug-related by the investigator and most were COVID-19 related.

At the recommendation of an independent Data Monitoring Committee and in consultation with the U.S. Food and Drug Administration (FDA), recruitment into the study was stopped early due to these positive results. These interim analysis results form the basis of Merck's application for Emergency Use Authorization (EUA) and are summarized in the Advisory Committee Briefing Document.

Clinical data are now available for all 1433 randomized participants in Protocol 002. Summaries of the baseline characteristics, efficacy and safety results for the full population are provided in this addendum. These data support the overall favorable benefit-risk assessment of molnupiravir for the treatment of mild to moderate COVID-19 in adults at high risk for disease progression. The formal evaluation of efficacy is considered complete at the planned interim analysis at which time the statistical criterion for success was met. The analyses of data for the full population are considered supportive analyses.

2 BASELINE DEMOGRAPHICS AND CHARACTERISTICS

Overall, baseline demographic and disease characteristics for the full population were well balanced between the intervention groups. At baseline, in all randomized participants, the median age was 43 years (range:18 to 90); 49% of participants were male; 57% were White, 5% Black or African American, 3% Asian, and 50% Hispanic or Latino. Forty-seven percent of participants 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%).

3 EFFICACY SUMMARY

Treatment with molnupiravir significantly reduced the risk of hospitalization or death through Day 29. **Table 1** provides the percentage of participants who were hospitalized or died through Day 29 due to any cause.

Table 1

Efficacy Results in Non-Hospitalized Adults with COVID-19 (Protocol 002 – Full Population)

	Molnupiravir (N=709) n (%)	Placebo (N=699) n (%)	Risk Difference* (95% CI)	p-value†
All-cause hospitalization or death through Day 29	48 (6.8)	68 (9.7)	-3.0 (-5.9, -0.1)	0.0218
Hospitalization‡	48 (6.8)	67 (9.6)		
Death	1 (0.1)	9 (1.3)		
Unknown§	0 (0.0)	1 (0.1)		

* Risk difference of molnupiravir-placebo based on Miettinen and Nurminen method stratified by time from COVID-19 symptom onset (≤3 days vs. >3 [4-5] days).
† 1-sided nominal p-value. (Definitive hypothesis test occurred at the prospectively defined interim analysis when the efficacy boundary was crossed and efficacy was formally demonstrated.)
‡ Defined as ≥24 hours of acute care in a hospital or an acute care facility (e.g., emergency room).
§Participants with unknown survival status at Day 29 are counted as having an outcome of all-cause hospitalization or death in the efficacy analysis.
Note: All participants who died through Day 29 were hospitalized prior to death.

4 SAFETY SUMMARY

Molnupiravir 800 mg orally twice daily for 5 days was generally well tolerated. A summary of AEs reported while participants were on study intervention or within 14 days of study intervention completion/discontinuation for all participants as treated is provided in **Table 2**. Discontinuation of study intervention due to an adverse event occurred in 1% of participants receiving molnupiravir and 3% of participants receiving placebo. Serious adverse events occurred in 7% of participants receiving molnupiravir and 10% receiving placebo; only one SAE (in the placebo arm) was considered drug-related by the investigator and most SAEs were COVID-19 related. Adverse events leading to death occurred in 2 (<1%) of the participants receiving molnupiravir and 12 (2%) of participants receiving placebo.

Table 2

Adverse Events Summary (Protocol 002 – Full Population)

	Molnupiravir		Placebo		Difference in % vs Placebo
	n	(%)	n	(%)	Estimate (95% CI)[a]
Participants in population	710		701		
with one or more adverse events	216	(30.4)	231	(33.0)	-2.5 (-7.4, 2.3)
with no adverse event	494	(69.6)	470	(67.0)	2.5 (-2.3, 7.4)
with drug-related[b] adverse events	57	(8.0)	59	(8.4)	-0.4 (-3.3, 2.5)
with serious adverse events	49	(6.9)	67	(9.6)	-2.7 (-5.6, 0.2)
with serious drug-related adverse events	0	(0.0)	1	(0.1)	-0.1 (-0.8, 0.4)
who died	2	(0.3)	12	(1.7)	-1.4 (-2.7, -0.5)
discontinued drug due to an adverse event	10	(1.4)	20	(2.9)	-1.4 (-3.1, 0.1)
discontinued drug due to a drug-related adverse event	4	(0.6)	3	(0.4)	0.1 (-0.8, 1.1)
discontinued drug due to a serious adverse event	5	(0.7)	13	(1.9)	-1.2 (-2.5, 0.0)
discontinued drug due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0.0 (-0.5, 0.5)

[a] Based on Miettinen & Nurminen method.
[b] Determined by the investigator to be related to the drug.

The most common adverse reactions in the molnupiravir treatment group are presented in **Table 3**, all of which were Grade 1 (mild) or Grade 2 (moderate).

Table 3

Adverse Reactions Occurring in Greater Than or Equal to 1% of Participants Receiving Molnupiravir (Protocol 002)*

	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.

Selected laboratory abnormalities reported through Day 29 are presented in **Table 4**.

Table 4

Selected Grade 3 and Grade 4 Laboratory Abnormalities (Protocol 002 – Full Population)

Criterion*	Molnupiravir N = 710 %	Placebo N = 701 %
Chemistry		
Alanine Aminotransferase (IU/L)		
Grade 3: 5.0 - <10.0 x ULN	1%	2%
Grade 4: ≥10.0 x ULN	<1%	0%
Aspartate Aminotransferase (IU/L)		
Grade 3: 5.0 - <10.0 x ULN	1%	<1%
Grade 4: ≥10.0 x ULN	0%	0%
Creatinine (mg/dL)		
Grade 3: >1.8 - <3.5 x ULN or Increase to 1.5 to <2.0 x above baseline	2%	2%
Grade 4: ≥3.5 x ULN or Increase of ≥2.0 x above baseline	<1%	1%
Lipase (IU/L)		
Grade 3: 3.0-<5.0 x ULN	<1%	<1%
Grade 4: ≥5.0 x ULN	0%	1%
Hematology		
Hemoglobin (g/dL)		
Grade 3: Male: 7.0 - <9.0 Female: 6.5 - <8.5	<1%	1%
Grade 4: Male: <7.0 Female: <6.5	0%	0%
Platelets (10^9/L)		
Grade 3: 25 - <50	0%	0%
Grade 4: <25	0%	<1%
Leukocytes (10^9/L)		
Grade 3: 1.000 – 1.499	<1%	<1%
Grade 4: <1.000	0%	0%

*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 1 post-baseline laboratory value had to be present. Only participants with a worsened grade from baseline were included.
Grades are based on the NIH DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 or predefined limit of change (PDLC).
ULN = Upper limit of normal range.

As shown in **Table 4**, Grade 3 and 4 decreases in hemoglobin were uncommon. Grade 1 and 2 decreases in hemoglobin (i.e., 8.5 – 10.4 g/dL in females and 9.0 – 10.9 g/dL in males)

were reported in 4% of participants receiving molnupiravir and 2% of participants receiving placebo.

5 CONCLUSION

There is an urgent unmet need for safe and effective oral agents for the treatment of COVID-19 in non-hospitalized patients, especially in the context of an ongoing pandemic with emergence of SARS-CoV-2 variants of concern. The risk-benefit assessment of molnupiravir supports an EUA for molnupiravir under Section 564 of the Federal Food, Drug, and Cosmetic Act.