Molnupiravir

Section last reviewed and updated 12/28/2021

Last literature search conducted 12/28/2021

Recommendation (NEW): In ambulatory patients (>/= 18 years) with mild to moderate COVID-19 at high risk for progression to severe **disease who have no other treatment options*, the IDSA guideline panel suggests molnupiravir initiated within 5 days of symptom onset rather than no molnupiravir. (Conditional recommendation, Low certainty of evidence)**

Remarks:

- Patients who put a higher value on the putative mutagenesis, adverse events or reproductive concerns, and a lower value on the uncertain benefits, would reasonably decline molnupiravir.
- Molnupiravir 800 mg for 5 days
- Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive molnupiravir.
- Molnupiravir is not authorized under the FDA EUA for use in patients < 18 years, because it may affect bone and cartilage growth.
- Molnupiravir is not recommended under the FDA EUA for use during pregnancy.
- Molnupiravir is not authorized under the FDA EUA for pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19, because benefit of treatment has not been observed in individuals when treatment is started after hospitalization due to COVID-19.

* Other options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, and neutralizing monoclonal antibodies. Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.

Figure 1. FDA EUA criteria for the use of molnupiravir[1]

Molnupiravir may only be used for the 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, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Patients And Caregivers: Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019 (COVID-19). Available at: https://www.fda.gov/media/155055/download. Accessed 28 December 2021.

Why is molnupiravir considered for treatment?

Molnupiravir is an oral antiviral that targets the genetic machinery that is responsible for SARS COV-2 replication. Molnupiravir is an oral pro-drug that is converted to β-D-N4 - hydroxycytidine (NHC) which acts as a substrate for RNA-dependent RNA polymerase. After it is incorporated into the viral RNA, serial mutations develop, resulting in a virus that is less fit for ongoing viral replication. One phase 1 RCT evaluated the safety and tolerability of molnupiravir in healthy adults without COVID-19 [1]. The study reported molnupiravir to be well tolerated, with no increased reports of serious adverse events among persons in the molnupiravir arm compared to those receiving placebo. The U.S. Food and Drug Administration (FDA) granted emergency use authorization (EUA) to molnupiravir on December 23, 2021, for the treatment of mild-to-moderate COVID-19 in adults (≥18 years) who are at high risk for progression to severe COVID-19, including hospitalization or death.

Summary of the evidence

Two RCTs reported on treatment of unvaccinated patients with COVID-19 with either 800 mg of molnupiravir or placebo for five days [2-3]. In one phase 3 trial (MOVe-OUT trial) reporting on the outcomes of death, hospitalization and serious adverse events, patients with mild-to-moderate COVID-19 received either molnupiravir or placebo within 5 days after the onset of symptoms. In the phase 2a trial reporting on the outcomes of death and serious adverse events in patients with symptom duration <7 days received molnupiravir or placebo.

Benefits

COVID-19-related mortality may be lower in patients receiving molnupiravir rather than placebo (RR: 0.11; 95% CI: 0.01, 0.86; low CoE). Similarly, COVID-19-related hospitalizations and the composite of all-cause hospitalization or death may trend towards a reduction among patients receiving molnupiravir rather than no molnupiravir (RR: 0.68; 95% CI: 0.48, 1.00; low CoE and HR: 0.69; 95% CI: 0.48, 1.01; low CoE, respectively).

Harms

Patients treated with molnupiravir may not experience greater serious adverse events than those receiving placebo (RR: 0.43; 95% CI: 0.17, 1.11; low CoE).

Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals [4]. Other concerns with molnupiravir include the possibility of viral mutagenesis in persons with compromised immune systems who are unable to clear the virus. Females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for 4 days after the last dose. Men of reproductive potential who are sexually active with females of childbearing potential should be counseled to use a reliable method of contraception during treatment and for at least three months after the last dose of molnupiravir. It is also not recommended in children <18 years of age for the concern of bone growth.

Molnupiravir does not require renal or hepatic dose adjustment.

Other considerations

The panel agreed that the overall certainty of evidence for treatment of ambulatory patients was low, given concerns with imprecision, driven by few reported events and a relatively small effect.

The use of molnupiravir presents additional considerations and potential concerns regarding viral mutagenesis in immunocompromised persons and safety in persons of reproductive age, for which more data are needed to quantify such effects. The panel recognized that alternative treatment options exist with the possibility of greater benefit with a smaller known safety profile. The FDA required the manufacturers to conduct additional animal studies on the impact of the drug on spermatogenesis and to establish a pregnancy registry if the drug was inadvertently administered during pregnancy.

The evidence confirms that using molnupiravir early in the disease process when viral loads are high confers maximum benefit. It is critical to make a rapid diagnosis and treat ambulatory patients with COVID-19 early in the disease course.

Conclusions

The guideline panel suggests the use of molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who are within 5 days of symptom onset and have no other treatment options. More data are needed on the potential adverse effects of this medication. The evidence supporting this recommendation will be reassessed with the release of updated published information from the MOVe-OUT study and other trials.

Question: Molnupiravir compared to no molnupiravir for ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease (v1)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	molnupiravir	no molnupiravir	Relative (95% CI)	Absolute (95% CI)		
COVID-19-related mortality (follow-up: range 28 days to 29 days)												
2[1,2]	randomised trials	not serious	not serious	not serious[a]	very serious[b,c]	none	1/764 (0.1%)	9/761 (1.2%)	**RR 0.11** (0.01 to 0.86)	**11 fewer per 1,000** (from 12 fewer to 2 fewer)	⨁⨁◯◯ Low	CRITICAL
COVID-19-related hospitalizations (follow-up: 29 days)												
1[1]	randomised trials	not serious	not serious	not serious[d,e]	very serious[c,f]	none	45/709 (6.3%)	64/699 (9.2%)	**RR 0.68** (0.48 to 1.00)	**29 fewer per 1,000** (from 48 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Hospitalization or death (all-cause) (follow-up: 29 days)												
1[1]	randomised trials	not serious	not serious	not serious[e]	very serious[b,c]	none	48/709 (6.8%)	68/699 (9.7%)	**HR 0.69** (0.48 to 1.01)	**29 fewer per 1,000** (from 49 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events (follow-up: range 28 days to 29 days)												
2[1,2]	randomised trials	not serious	not serious	not serious	very serious[f,g]	none	6/765 (0.8%)	14/763 (1.8%)	**RR 0.43** (0.17 to 1.11)	**10 fewer per 1,000** (from 15 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings are derived from evidence that has not been peer reviewed or published.

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

a. In Bernal 2021, after day 29, one additional death resulting from adverse events occurred in the molnupiravir group and three additional deaths occurred in the placebo group. In Fischer 2021, at day 31, one additional death resulting from hypoxia occurred in the placebo group.
b. Small number of events; fragility present.
c. 95% CI cannot exclude no meaningful benefit.
d. COVID-19 related hospitalizations is a surrogate for ICU admission, mechanical ventilation and death. Not rated down.
e. All 10 patients reported as died at day 29 had been hospitalized.
f. Small number of events.
g. 95% CI cannot exclude the possibility of harms.

References

1. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et. al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2021: Available at: https://www.nejm.org/doi/10.1056/NEJMoa2116044 [Epub ahead of print 16 December 2021].
2. Fischer WA, Eron Jr JJ, Holman W, et. al. A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med 2021. Available at: https://www.science.org/doi/10.1126/scitranslmed.abl7430 [Epub ahead of print 23 Dec 2021].

References

1. Painter WP, Holman W, Bush JA, et. al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. Antimicrob Agents Chemother **2021**; 65(5): e02428-20.
2. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et. al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med **2021**: Available at: https://www.nejm.org/doi/10.1056/NEJMoa2116044 [Epub ahead of print 16 December 2021].
3. Fischer WA, Eron Jr JJ, Holman W, et. al. A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med **2021**. Available at: https://www.science.org/doi/10.1126/scitranslmed.abl7430 [Epub ahead of print 23 Dec 2021].
4. U.S. Food and Drug Administration. Fact Sheet for Patients And Caregivers: Emergency Use Authorization (EUA) Of Molnupiravir For Coronavirus Disease 2019 (COVID-19). Available at: https://www.fda.gov/media/155055/download. Accessed 28 December 2021.

Supplementary Materials

Study characteristics

- **Table s1.** Molnupiravir vs. no molnupiravir for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease

Forest Plots

- **Figure s1.** Meta-analysis of molnupiravir on the outcome of mortality
- **Figure s2.** Meta-analysis of molnupiravir on the outcome of serious adverse events

Risk of bias

- **Table s2.** Randomized controlled studies (molnupiravir vs. no molnupiravir)

Table s1. Molnupiravir vs. no molnupiravir for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease

Study/ year	Country/ hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD)/ median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Bernal 2021	107 sites in 20 countries	RCT	1433 (716/717)	51.3	43.0 (Range: 18-90)	Ambulatory adults with mild or moderate COVID-19 (at least 1 symptom) with a positive SARS CoV-2 test within 5 days and at least one risk factor for the development of severe disease	Molnupiravir 800 mg twice daily for 5 days	Placebo	Standard of care including: antipyretics, anti-inflammatory agents, glucocorticoids)	Mortality Hospitalization Rate of hospitalization Clinical improvement Serious adverse events	Merck
Fisher 2021	10 sites in US	RCT	202	51.5	Age: Median (range by treatment arm) Molnupiravir 200 mg: 32 (19-65) Molnupiravir 400 mg: 42.5 (19-82) Molnupiravir 800 mg: 42 (18-68) Placebo: 39 (19-71).	Unvaccinated adults if they had a positive test for SARS CoV-2 infection within 96 hours and had onset of symptoms within 7 days of treatment initiation	Molnupiravir 200 mg every 12 hours x 5 days Molnupiravir 400 mg every 12 hours x 5 days Molnupiravir 800 mg every 12 hours day x 5 days	Placebo	None	Mortality Change in SARS-CoV-2 viral load from baseline Median time to COVID-19 symptom resolution Isolation of infectious virus SAEs	Merck and Ridgeback Biotherapeutics

Figure s1. Meta-analysis of molnupiravir on the outcome of mortality

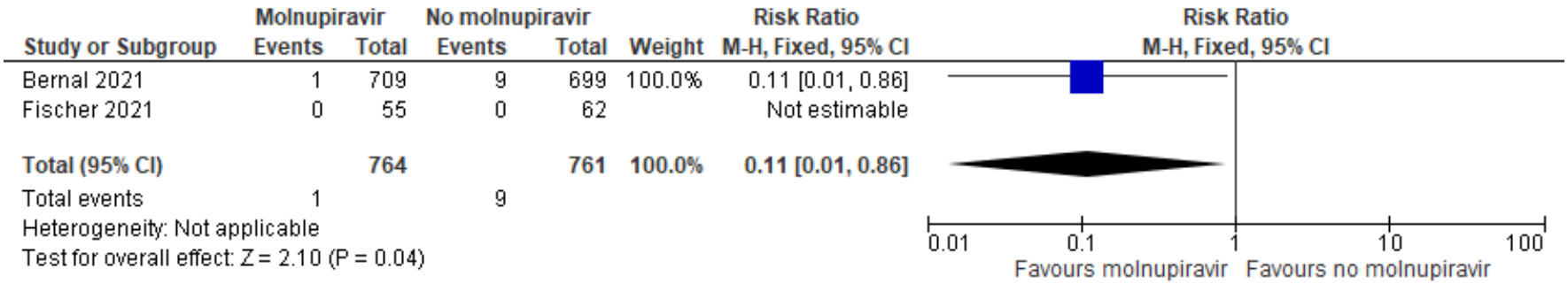

Figure s2. Meta-analysis of molnupiravir on the outcome of serious adverse events

Table s2. Randomized controlled studies (molnupiravir vs. no molnupiravir)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bernal 2021							
Fischer 2021							

Low	High	Unclear

References for Supplementary Materials

1. Fischer WA, Eron Jr JJ, Holman W, et. al. A Phase 2a clinical trial of Molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. Sci Transl Med 2021. Available at: https://www.science.org/doi/10.1126/scitranslmed.abl7430 [Epub ahead of print 23 Dec 2021].
2. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et. al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2021: Available at: https://www.nejm.org/doi/10.1056/NEJMoa2116044 [Epub ahead of print 16 December 2021].