

Molnupiravir: mutagenic, carcinogenic, authorized in the UK

Leo Goldstein¹, defyccc.com

November 6, 2021

The UK authorization of Molnupiravir for mild/moderate COVID-19¹ says a lot about the current COVID-19 derangement syndrome. Molnupiravir's efficacy is marginal, but its mutagenicity and carcinogenicity are real. The tidbits of information published by the UK's MHRA include bone marrow toxicity discovered in some early trials, something suggested earlier in an article² on this site. Thus, Molnupiravir is likely to cause leukemia.

The re-analysis of the data in Merck's press release from October³, suggests that the announced results show much lower efficacy than claimed, even without questioning the conduct of the trial and reporting. Merck's failure to publish that data is alarming. Merck also failed to disclose the outcomes from patients who were recruited after the cut-off date for the intermediate review.

The UK authorization also reveals that the population in Merck's trial was younger and less at risk than the general population. When treated with Molnupiravir, the trial population had worse outcome than the comparable general population not treated with Molnupiravir.

These facts are grounds for Molnupiravir's rejection, not approval.

Bone Marrow Toxicity and Leukemia Potential

The UK regulator MHRA referenced¹ the following results from a previous study in dogs (emphasis is added):

*“Reversible, dose-related **bone marrow toxicity** affecting all haematopoietic cell lines was observed in **dogs** at ≥ 17 mg/kg/day (**0.4 times the human NHC exposure** at the recommended human dose (RHD)).”*

0.4 times exposure can be rephrased as a *comparable exposure*. Molnupiravir's mutagenic effects can best be compared to the effects of ionizing radiation. A short-term exposure causes transitory injury, which may not even be felt. The long-term effects, depending on the dose, include cancer. The observed bone marrow toxicity suggests future leukemia.

¹ Contact ah@defyccc.com

Can be cited as Goldstein L., *Molnupiravir: mutagenic, carcinogenic, authorized in the UK*, TrialSite News, <https://trialsitenews.com/molnupiravir-mutagenic-carcinogenic-authorized-in-the-uk/>, 2021

The information about bone marrow toxicity was in the preprint of the original study ⁴ but mysteriously disappeared in the published article ⁵. Notably, the first author of the paper is a C-level executive in the Ridgeback Biotherapeutics LP, Merck's partner in Molnupiravir.

More Trial Oddities

Merck's press release³ announced "successful trial results" in 775 patients. It also announced the end of enrollment of new patients, after the study had already enrolled more than 90% of prospective patients (or ~1,400). Because of the short observation time of 29 days, including the five days of treatment, Merck now has complete results from all ~1,400 patients (the original 775 plus those recruited after the interim analysis). Yet, none of this data has been published. That further raises suspicions that the data does not support Merck's claims.

Selection of Low-Risk Patients

MHRA authorized Molnupiravir for adults with "*at least one risk factor for developing severe illness*", but the risk factors include non-severe obesity and age (above 60), and some other conditions that can be mild or severe. This covers most of the adult population.

Merck's press release gives the impression that the trial population was a high-risk population. In fact, the study patients were at lower risk than the general population¹ (emphasis is added):

*"At baseline, in all randomised subjects, the **median age was 44 years** (range: 18 to 88 years); **14% of subjects were 60 years of age or older and 3% were over 75 years of age; ...**"*

More than 30% of the general adult population is 60 years old or older, compared with only 14% in the study population. 86% of the subjects were ages 18 - 59. They had at least one of the following conditions: "*diabetes, obesity (BMI >30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer.*" Except for obesity, no information about the severity of these conditions is available. More than 40% of the US population 18 - 59 are obese (BMI>30), per ref ⁶, Table. 2. Non-severe obesity (35>BMI>30) increases the risk of COVID-19 hospitalization by only 7% ⁷.

Even with this questionable patient selection, the rate of hospitalization in the Molnupiravir treatment group was 7.8%. This is **higher** than the hospitalization rate of less than 7%, found in the general population in January 2021. This is **significantly higher** than the hospitalization rate of the general population in the time of the trial (although it is hard to compare because of the lack of data from the trial).

Absence of Rationale to Stop the Trial Prematurely

The truncation of the trial was not justified. Although the efficacy was reported as 48% (relative risk reduction or RRR), the lower bound of the 95% confidence interval was only **17%** (per ref ¹, Table 2). For a novel drug with potentially very serious adverse effects, this is an unsatisfactory result.

It is known in the industry that truncated trials significantly overestimate the effect⁸. When applying this overestimation to this trial, the estimated RRR drops to **27%**, and lower bound to **<0** (i.e., worsened outcome).

Thus, the results of intermediary analysis did not justify stopping the trial. The decision to stop recruiting was made after more than 90% of the planned number of participants were already recruited. If the sponsor believed that the drug is effective and safe for the intended population, they should have spent another 5-6 weeks to complete the study as planned⁹. That would have provided more necessary data, increased the lower bound of RRR confidence interval, and eliminated the controversy with the trial's truncation. None of the justifications for truncating the trial were valid. Even taken as is, the efficacy data from the interim analysis was not sufficient for Molnupiravir's authorization.

Additional problems with this trial have already been identified². Based on all the inconsistencies in the conduct and reporting of this trial, it should be treated as scientific fraud.

Remarks

This reckless approval might have been influenced by the UK government's February 2021 promise¹⁰ to fast track certain COVID-19 treatments, including Molnupiravir.

At this point, one should not be surprised by what was **not** tested, according to MHRA¹:

“Carcinogenicity studies with molnupiravir have not been conducted.”

“No drug interactions have been identified based on the limited available data.”

“No clinical interaction studies have been performed with molnupiravir.”

Doctors continue to warn about the risks of Molnupiravir¹¹.

The concerns about the global catastrophic danger of Molnupiravir¹² have not been addressed.

References

1. MHRA. Summary of Product Characteristics for Lagevrio. GOV.UK <https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio> (2021).
2. Goldstein, L. Merck Ignores Molnupiravir's Cytotoxicity. *TrialSite News*. <https://trialsitenews.com/merck-ignores-molnupiravirs-cytotoxicity> (2021).
3. Merck. Merck and Ridgeback's Investigational Oral Antiviral Molnupiravir Reduced the Risk of Hospitalization or Death by Approximately 50 Percent Compared to Placebo for Patients with Mild or Moderate COVID-19 in Positive Interim Analysis of Phase 3 Study. *Merck.com* <https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/> (2021).
4. Painter, W. P. *et al.* Human Safety, Tolerability, and Pharmacokinetics of a Novel Broad-Spectrum Oral Antiviral Compound, Molnupiravir, with Activity Against SARS-CoV-2. 2020.12.10.20235747 <https://www.medrxiv.org/content/10.1101/2020.12.10.20235747v1> (2020) doi:10.1101/2020.12.10.20235747.
5. Painter, W. P. *et al.* Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity against SARS-CoV-2. *Antimicrobial Agents and Chemotherapy* **65**, e02428-20 <https://journals.asm.org/doi/full/10.1128/AAC.02428-20> (2021).
6. CDC. Products - Health E Stats - Prevalence of Overweight, Obesity, and Extreme Obesity Among Adults Aged 20 and Over: United States, 1960–1962 Through 2017–2018. <https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm> (2021).
7. Kuehn, B. M. More Severe Obesity Leads to More Severe COVID-19 in Study. *JAMA* **325**, 1603 (2021).
8. OrthoEvidence. Overestimating the Treatment Effects of Molnupiravir Against COVID-19: A Deep Look from the Perspective of Stopping-Trial-Early-For-Benefits. <https://myorthoEvidence.com/Blog/Show/153> (2021).
9. Merck Sharp & Dohme Corp. 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. <https://clinicaltrials.gov/ct2/show/NCT04575597> (2021).
10. UK Dept of H&SC. Groundbreaking COVID-19 treatments to be fast-tracked through clinical trials. GOV.UK <https://www.gov.uk/government/news/groundbreaking-covid-19-treatments-to-be-fast-tracked-through-clinical-trials> (2021).
11. Schalkwyk, J. M. van. Buyer beware: molnupiravir may damage DNA. *BMJ* **375**, n2663 <https://www.bmj.com/content/375/bmj.n2663> (2021).

12. Goldstein, L. Is Molnupiravir a Global Catastrophic Threat? *TrialSite News*.
<https://trialsiteneeds.com/is-molnupiravir-a-global-catastrophic-threat> (2021).