Re-analysis of Molnupiravir Trials, Phase II/III

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Abstract

This is a re-analysis of the data from Molnupiravir trials, presented by the FDA.

The trials' sponsor modified the pre-registered protocol, so the results will appear more beneficial than they are. To this end, results from patients recruited by August 5 were reported as a separate trial – here referred to as Trial 1. Thus, the data from patients recruited after August 5 should also be presented as a separate trial – here referred to as Trial 2.

In this second trial, the Molnupiravir arm had **32.5% higher relative risk** of hospitalization or death compared to the placebo arm.

Both trials show that starting Molnupiravir treatment later (more then 3 days after symptom onset) is associated with better outcomes than starting the treatment earlier (less then 3 days from symptom onset). This is consistent with the hypothesis that Molnupiravir harms the patient synergistically with the coronavirus.

These results clearly show that Molnupiravir is not an effective treatment and/or prophylaxis for COVID-19.

Introduction

The FDA has published the data submitted to it by Merck and Ridgeback Biotherapeutics (together referred to as "the sponsor") for their Molnupiravir trial(s) [1] [2].

The sponsor arbitrarily decided to truncate the registered trial NCT04575597 after an interim review. It stopped recruiting after about 90% of the planned participants had been recruited. The sponsor then reported the results from patients recruited before August 5 as a separate trial - Part 1 Trial (or Trial 1). Thus, the data from patients recruited after August 5 should also be presented as a separate trial - Part 2 Trial (or Trial 2). Causing further confusion, the FDA published data bits from Trial 1 separately[1], and from Trial 1 and Trial 2 combined[2].

Methods

This paper re-analyzes the data reported by the FDA on behalf of the sponsor.

In **Table 1** below, the numbers for Trial 2 are calculated by deducting the numbers for Trial 1 (Table 1 in the FDA's Briefing Document[1]) from the respective total numbers (Table 1 in the FDA's Addendum[2]).

Results

Table 1. Incidence of the event (hospitalization or death) in the Molnupiravir trials

Drug		RRR	MLNP			Placebo		
Outcome			**rate**	**Event**	**OK**	**rate**	**Event**	**OK**
Trial 2	**Total**	**-32.5%**	**6.17%**	20	324	**4.66%**	15	322
	<=3d	**-80.0%**	**6.00%**	9	150	**3.33%**	5	150
	>3d	**-8.7%**	**6.32%**	11	174	**5.81%**	10	172
	<=60	**-15.4%**	**5.08%**	13	256	**4.40%**	11	250
	>60	**-85.3%**	**10.29%**	7	68	**5.56%**	4	72
Trial 1	**Total**	48.3%	**7.27%**	28	385	**14.06%**	53	377
	<=3d	31.9%	**8.47%**	16	189	**12.43%**	23	185
	>3d	60.8%	**6.12%**	12	196	**15.63%**	30	192
	<=60	46.1%	**6.87%**	23	335	**12.73%**	41	322
	>60	54.2%	**10.00%**	5	50	**21.82%**	12	55
Both Trials	**Total**			48	709		68	699
	<=3d			25	339		28	335
	>3d			23	370		40	364
	<=60			36	591		52	572
	>60			12	118		16	127

In Trial 2, Molnupiravir **increased** the relative risk of hospitalization or death by almost 33%. One person died in each of the arms, Molnupiravir and placebo.

Both trials show significantly worse results when the drug is administered within 3 days of symptom onset, as opposed to later (i.e., 4-5 days). In Trial 2, the reported RRR was about -90% and -9%, respectively. In Trial 1, the reported RRR was about 30% and 60% for administering the treatment <=3 days and >3 days from symptom onset, respectively. All antivirals are more effective when used earlier. This effect should be even greater for Molnupiravir, given the drug's mechanism of action. Lethal mutagenesis is a lengthy process. It slowly degrades the fitness of the viral population[3] (except when it improves it [4 5]). Thus, Molnupiravir is expected to show better results in early treatment. But the data shows the opposite, contradicting the hypothesis about Molnupiravir's effect against SARS-COV-2.

Another unreported feature of these trials was that the patients were low to medium risk, contrary to the sponsor's statement. Only 17% (245/1408) of the participants were over 60. Majority of the rest were reported as obese (BMI > 30), but this condition is shared by 40% of the US population 18 - 59 (ref. [6], Table. 2). Moderate obesity increases the risk of COVID-19 hospitalization by only 7% [7], which does not put them in the high risk group. The study participants were probably at lower risk than the general hospitalized population. The trials were conducted in 173 locations, very few of which were in the North America and Western Europe, so more accurate comparison is impossible.

The average hospitalization rates in Trial 1 where 7.8%, which is too high. Anyway, the results suggest that is much higher than in the general US population and puts the results of Trial 1 in doubt. Also, the death rate 2.1% (8/377) among placebo patients was way too high for the low/medium risk population. It might be explained as a clerical error. Thus, the results of Trial 1 should be rejected because of errors.

Of notice, the protocol included only double blinding. The assessors were not blinded.

Discussion

The most likely explanation of these results is that Molnupiravir degrades the host's immune system, rather than SARS-COV-2 population. Molnupiravir exhibits bone marrow toxicity [8 9], possibly interfering with B-cells production. In low risk to moderate risk patients, the specific immune response starts with the symptoms, and eliminates the infectious virus after 6-9 days[10]. When Molnupiravir is started early, it suppresses the immune system before the immune system can suppress virus. When Molnupiravir is started later, the immune system has time to neutralize the infectious virus before being temporarily suppressed by Molnupiravir.

Another possibility is that the rapidly mutating coronavirus, created by Molnupiravir, evades, suppresses, or confuses the immune system. Most of SARS-COV-2 non-structural proteins inhibit the host's immune system in some way [11]. These may be produced in higher amounts if a Molnupiravir caused mutation prevents the assembly of the whole virion.

Obviously, Trial 1 and Trial 2 cannot be combined and reported as one trial. The sponsor decided to break it into two[12]. Trial 2 is more representative because it was conducted later and has more reasonable total hospitalization rate and death rate.

The acute bone marrow toxicity of Molnupiravir indicates that it is carcinogenic and is likely to cause leukemia in the long run.

The Molnupiravir's lack of efficacy is in line with the results of its trials in animals [13].

Conclusion

Molnupiravir has not been shown effective in treating or preventing COVID-19 and may have harmful side effects and consequences.

No Competing Interests

The author declares no competing interest. No funding was provided for this work.

References

1. FDA CDER Briefing. FDA Briefing Document. Published online November 26, 2021. https://www.fda.gov/media/154418/download

2. FDA CDER Briefing Addendum. FDA Addendum to Briefing Document. Published November 26, 2021. https://www.fda.gov/media/154419/download

3. Belshaw R, Gardner A, Rambaut A, Pybus OG. Pacing a small cage: mutation and RNA viruses. *Trends Ecol Evol*. 2008;23(4):188-193. doi:10.1016/j.tree.2007.11.010

4. Elena SF, Sanjuán R. Virus Evolution: Insights from an Experimental Approach. *Annu Rev Ecol Evol Syst*. 2007;38(1):27-52. doi:10.1146/annurev.ecolsys.38.091206.095637

5. Anciaux Y, et al. Evolutionary Rescue over a Fitness Landscape. *Oxf Acad*. Published online March 13, 2018. https://academic.oup.com/genetics/article/209/1/265/5931020

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. Published February 5, 2021. https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/obesity-adult.htm

7. Kuehn BM. More Severe Obesity Leads to More Severe COVID-19 in Study. *JAMA*. 2021;325(16):1603. doi:10.1001/jama.2021.4853

8. MHRA. Summary of Product Characteristics for Lagevrio. GOV.UK. Published November 4, 2021. https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio

9. Goldstein L. Molnupiravir: mutagenic, carcinogenic, authorized in the UK. *TrialSite News*. Published online November 6, 2021. https://trialsitenews.com/molnupiravir-mutagenic-carcinogenic-authorized-in-the-uk/

10. FLCCC Alliance. FLCCC Protocols - A Guide to the Management of COVID-19. Published online November 12, 2021. https://covid19criticalcare.com/wp-content/uploads/2020/12/FLCCC-Protocols-%E2%80%93-A-Guide-to-the-Management-of-COVID-19.pdf

11. Martin-Sancho L, Lewinski MK, Pache L, et al. Functional landscape of SARS-CoV-2 cellular restriction. *Mol Cell*. 2021;81(12):2656-2668.e8. doi:10.1016/j.molcel.2021.04.008

12. 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. Published October 1, 2021. 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/

13. Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Sci Transl Med*. 2020;12(541):eabb5883. doi:10.1126/scitranslmed.abb5883

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