Merck's Part 2 Trial Shows Molnupiravir is Inferior to Placebo

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Today, November 26, Merck and Ridgeback have issued a press release[1] providing the sum of the numbers for its Molnupiravir trials. The putative results of the Part 1 Trial (patients recruited through August 5) were announced in their October 1 press release[2]. The Part 2 Trial comprises patients recruited after August 5.

In the Part 2 Trial (patients recruited after August 5), Merck's Molnupiravir has shown inferior results compared with placebo: 6.2% (20/324) bad outcomes in the Molnupiravir group compared to 4.7% (15/322) bad outcomes in the placebo group. The bad outcome is defined as hospitalization or death. In each group, one patient died. Thus, Molnupiravir has increased chances of bad outcome by ~25%.

This result might be possibly explained by bone marrow toxicity of Molnupiravir [3] [4], hypothetically causing temporary immunosuppression in patients.

Also of note is the prevalence of the Delta variant in the Part 2 Trial. Delta variant exhibits faster growth and shorter incubation period compared with the wild type and earlier variants [5].

The Part 1 and Part 2 cannot be combined and treated as one trial, even as only one trial was registered. The sponsor decided to break it into parts, and to present and analyze the first part as a separate complete trial[2]. Thus, the second part should be also treated as a separate trial. The Part 2 Trial is more representative because it better corresponds to the current conditions, when almost all cases are Delta.

If one wants to combine its results with those from the Part 1 Trial, the only rigorous way to do so is a meta-analysis, discounting the Part 1 Trial because it is obsolete and has many other defects, and then accounting for the heterogeneity[6] between these trials.

The results of the Part 2 Trial are also more in agreement with the theory and experience of the lethal mutagenesis, the mechanism of Molnupiravir action. Lethal mutagenesis works slowly[7] (if at all[8] [9]) and cannot be effective for an acute disease like COVID-19[10].

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Table 1. Calculation of the numbers in the Part 2 Trial from Merck's press release [1]

Drug	MLNP	MLNP	Placebo	Placebo
Outcome	**Bad**	**Good**	**Bad**	**Good**
Both Parts	48	709	68	699
	6.77%		9.73%	
Part 1 Trial	28	385	53	377
	7.27%		14.06%	
Part 2 Trial	20	324	15	322
	6.17%		4.66%	

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