Evaluate Vantage

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Merck boosts Pfizer’s Covid antiviral advantage

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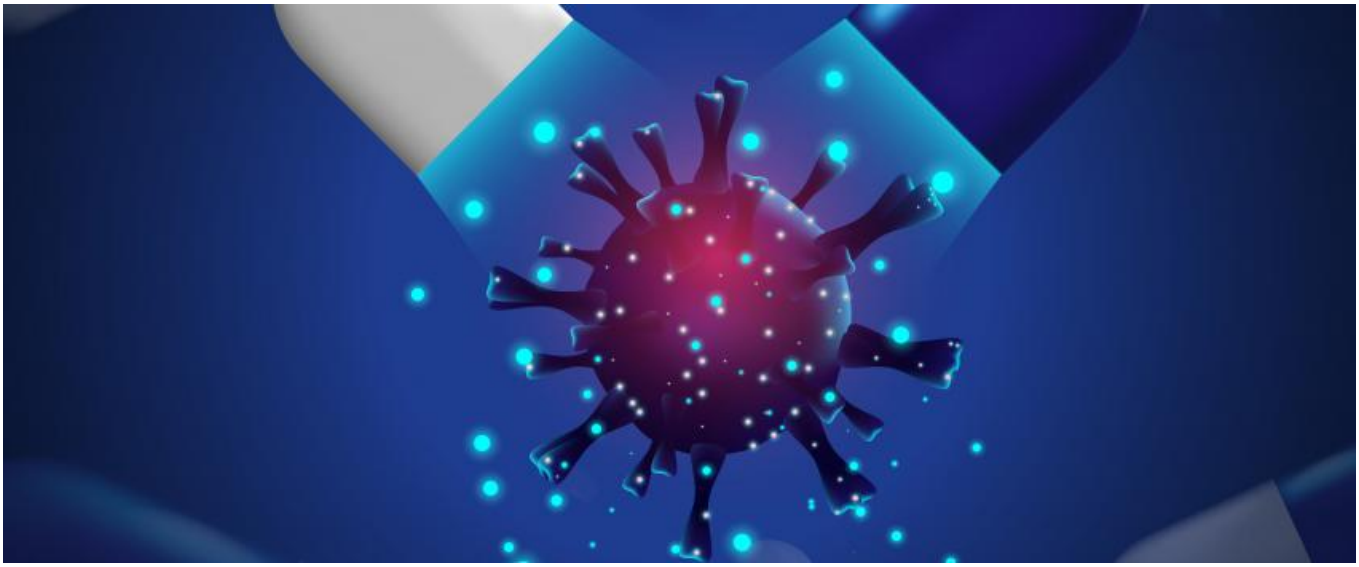

Efficacy of Merck/Ridgeback’s molnupiravir shows an alarming fall-off, just as a US regulatory panel review beckons.

As Tuesday’s US adcom over Merck & Co’s application for molnupiravir looms, anyone worrying that this Covid-19 antiviral was being eclipsed by Pfizer’s Paxlovid will have had these fears confirmed. Molnupiravir’s Move-Out trial today registered an alarming fall in efficacy at its final analysis.

A 48% reduction in risk of hospitalisation or death in mild-to-moderate Covid-19 outpatients at Move-Out’s interim analysis has melted away to just 30% at final readout, Merck revealed today. Were it not for Paxlovid’s 89% efficacy this would have dealt plans to contain the coronavirus’s spread a serious blow, especially as reports of a new variant emerge.

For Merck, of course, this is undeniably bad news. The group’s stock had fallen 10% when Move-Out’s interim hit was followed a month later by Pfizer unveiling Paxlovid’s 89% interim efficacy in the Epic-HR trial, and today it was trading down 5% while Pfizer opened up 6%.

Full data at adcom

Until today’s final analysis from Move-Out the most important dataset for the adcom was assumed to be the study’s interim analysis, toplined in October.

Today Merck confirmed that the final analysis just unveiled had been shared with the FDA and would also be presented to Tuesday’s antimicrobial drugs panel, which will review Merck’s application for molnupiravir’s emergency use authorisation.

The new data involve nearly double the number of patients considered at interim, and among these new subjects there were 20 additional 29-day hospitalisations or deaths in the molnupiravir cohort, versus just 15 in the control group.

This meaningfully cuts molnupiravir’s edge over control, though the study is still nominally positive and Merck says it continues to support molnupiravir’s benefit-risk for mild-to-moderate Covid-19 in adults at high risk of disease progression.

Oral Covid-19 antivirals: a cross-trial comparison		
	Active	**Control**
Molnupiravir (Merck & Co/Ridgeback), Move-Out study interim readout (Oct 1)		
Number of patients	385	377
Hosp or death at 29 days, for those treated ≤5 days from symptom onset	28	53
Death at 29 days, for those treated ≤5 days from symptom onset	0	8
Stats	Relative risk reduction 48% (p=0.0012)	
Molnupiravir (Merck & Co/Ridgeback), Move-Out study final analysis (Nov 26)		
Number of patients	709	699
Hosp or death at 29 days, for those treated ≤5 days from symptom onset	48	68
Death at 29 days, for those treated ≤5 days from symptom onset	1	9
Stats	Relative risk reduction 30%*	
Paxlovid (PF-07321332 + ritonavir; Pfizer), Epic-HR study interim readout (Nov 5)		
Number of patients	389	385
Hosp or death at 28 days, for those treated ≤3 days from symptom onset	3	27
Death at 28 days, for those treated ≤3 days from symptom onset	0	7
Stats	Relative risk reduction 89% (p<0.0001)	
*Note: *p=0.0218, but nominal only as statistical evaluation deemed complete when efficacy criterion was met at interim. Source: company statements.*		

Perhaps one question for the panel will be why efficacy seems to have dropped so drastically. Either the interim result was a fluke, or the final data are an aberration, or confounding factors came into play after recruitment into Move-Out was stopped when the interim analysis hit.

The study had aimed to recruit 1,850 patients, and the trigger for interim analysis was met with 762 evaluable. Enrolment was halted after the interim hit, but by then another 646 had already been enrolled (today's final analysis details 1,408 patients), so any subsequent treatments these extra 646 received after unblinding will have to be considered.

For comparison, Pfizer's Epic-HR had an enrolment target of 3,000, but interim efficacy was confirmed after an apparent 1,200 or so had reached a 28-day target. It is not clear at present how many more had already been enrolled at that point, when recruitment was similarly halted, or what their subsequent treatment might have involved, but clearly final data from Epic-HR could provide an interesting comparison.

Of course, it is likely that Epic-HR had rendered many such detailed considerations irrelevant, and before today's disappointment molnupiravir was already seen as a second-string Covid antiviral.

Big in the UK

Almost as a side note to Tuesday's adcom is the fact that the UK had become the first country to approve molnupiravir, as Lagevrio, on November 4 – one day before Pfizer toplined Epic-HR. And the country had already started stockpiling molnupiravir and Paxlovid before either was approved.

This points to a fundamental problem in that, however good Paxlovid is, there is currently not enough of it to go around. Molnupiravir might be worse, but this does not alter the fact that the world needs more Covid antivirals, and for some a substandard one might be better than none at all.

Perhaps this will be what determines whether the US ultimately authorises molnupiravir.

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