Evaluate Vantage

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Astra’s Covid-19 vaccine: much ado about nothing?

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With results of the full primary analysis now out the spotlight falls on a further 14 as yet unadjudicated Covid-19 cases.

This week’s storm over a US pivotal trial of the Covid-19 vaccine AZN1222 could be fizzling out. Astrazeneca this morning said the study’s final primary analysis yielded vaccine efficacy of 76% – only slightly below Monday’s disputed 79% interim figure.

If 76% efficacy is accurate the obvious question is what would have moved the NIAID to start its extraordinary row with the company. The spotlight is on Astra’s revelation of an extra 14 possible Covid-19 cases in the trial that have yet to be adjudicated. However, even if all occurred on AZN1222 – a highly unlikely worst-case scenario – the numbers do not change hugely, *Evaluate Vantage* calculates.

Certainly, the pressure is now on the NIAID to spell out its case to avoid further undermining confidence in the vaccine. That confidence has been shaken in no small part by Astra’s own evasiveness and lack of clarity at several points in AZN1222’s development (*Obfuscation and evasion: Astra shows how not to disclose data, March 23, 2021*).

The company is still not revealing the precise split of symptomatic Covid-19 cases in the pivotal US trial, for instance, saying only that 190 have now been adjudicated; Monday’s 79% efficacy figure had been based on 141.

Fortunately, making a few assumptions, the numbers can be calculated, and it appears that there were around 62 cases in the active cohort versus 128 on placebo. Perhaps Astra feared that a straight numerical comparison against Biontech/Pfizer or Moderna’s rival datasets would appear bad, but its trial had only half as many subjects given placebo as were assigned to AZN1222.

Breaking down AZN1222's US pivotal trial		
	Active	**Placebo**
Subjects enrolled (total 32,449, at 2:1 randomisation)	21,633	10,816
Symptomatic cases at interim (triggered at ~75 total cases, actually 141 adjudicated)	42	99
Vaccine efficacy at interim analysis	78.8%	
Severe cases in interim analysis	0	5
Symptomatic cases at primary (triggered at ~150 total cases, actually 190 adjudicated)	62	128
Vaccine efficacy at primary analysis	75.8%	
Severe cases in primary analysis	0	8
Note: apart from severe cases the cohort splits are based on Vantage assumptions.		

Importantly, all eight severe cases (there had been five at interim) occurred on placebo, so the group can still say AZN1222 offers 100% protection here.

Thus the concerns of the NIAID, echoing the trial's data-monitoring board, about Astra's interim data press release having possibly relied on "outdated information", appear groundless on seeing the updated dataset.

Unless, of course, a smoking gun can be found in the 14 further cases Astra today said might have accrued since the primary analysis was locked at 190.

However, this looks unlikely. For vaccine efficacy to go into the 69-74% range, which the Washington Post reported was what the data-monitoring board was claiming, most of the 14 new cases would have to have accrued in the active vaccine arm – this seems farfetched – and even a worst-case scenario does not take efficacy below 70%.

…and what about those 14 extra cases? Possible scenarios		
	Active	**Placebo**
Subjects enrolled (total 32,449, at 2:1 randomisation)	21,633	10,816
Symptomatic cases (total 204), worst case: all 14 in active arm	76	128
Worst-case vaccine efficacy	70.3%	
Symptomatic cases (total 204), mid case: 14 new cases split evenly	67	137
Mid-case vaccine efficacy	75.5%	
Symptomatic cases (total 204), best case: all 14 in placebo arm	62	142
Best-case vaccine efficacy	78.2%	
Source: Evaluate Vantage calculations.		

A final possibility is that something has occurred regarding severe Covid-19, such as one or more cases after

active vaccination. But this, like the above scenarios, remains conjecture, and a full and transparent analysis of the most up-to-date results from this trial might not emerge until the US FDA’s briefing documents.

In the meantime, public faith in Astra’s trouble-prone Covid-19 vaccine is unlikely to return any time soon.