Evaluate Vantage

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Five questions for Astrazeneca on its Covid-19 vaccine

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Outstanding issues include whether Astra can file AZD1222 in the US, and why a lower priming dose seemed to produce the best efficacy.

The third set of phase III Covid-19 vaccine data are in – and the market reaction was disappointment. Despite Astrazeneca talking up a lack of severe Covid-19 cases and hospitalisations in a pooled analysis of its UK and Brazil studies of AZD1222, the group's stock was down 3% today.

Astra has suffered from the fact that the average efficacy of AZD1222 in preventing Covid-19 infections, at 70%, is less impressive than the 95% seen with Pfizer/Biontech's and Moderna's candidates. But the Astra release, encompassing different data with two different dosing strategies, was also confusing.

In short, there are more questions than answers on AZD1222. Here are some of the key points that need to be clarified.

Why might a lower priming dose work better, and is this a real effect?

The pooled analysis involved the phase II/III COV002 trial in the UK and the phase III COV003 study in Brazil, and included 11,636 participants. The interim analysis was carried out once 131 cases of Covid-19 had occurred.

However, the results looked very different with two different dosing regimens.

Across the UK and Brazil trials, 8,895 people received a full-dose ($5x10^{10}$ viral particles) primer and booster at least a month apart. In these patients, efficacy at preventing Covid-19 was an unimpressive 62%.

However, in a subgroup of 2,741 participants in the UK study receiving a half-dose ($2.5\ x10^{10}$ viral particles) primer followed by a full-dose booster, efficacy was 90%. The addition of a half-dose regimen appeared to have come about because of a dosing error, according to Berenberg analysts.

"We think that by giving a smaller first dose we're priming the immune system differently – we're setting it up better to respond," said Professor Andrew Pollard, head of the Oxford Vaccine Group, during a media call today to discuss the data. However, he conceded that more work needed to be done to verify this theory.

Professor Pollard was confident that the effect was real rather than just a function of the small numbers of

participants involved in this analysis. There is also speculation that the full-dose primer might have raised too many antibodies to the adenovirus vector itself, and made the second dose less effective.

However, Leerink's Geoffrey Porges was scathing about this claim: "The suggestion by the inventors that the small sample given the lower priming dose was evidence of superior efficacy only brings discredit to the programme," he wrote.

For which dose(s) will Astra be seeking approval?

This ultimately appears to be down to the regulators, with Mene Pangalos, head of biopharmaceuticals R&D for Astra, saying the discussion would be around whether one dosing schedule, or both, could get the nod.

"The pooled analysis is sufficient for approval, we think, across a variety of regions including the EU and UK," he added. Astra has already started rolling reviews with the EU and UK regulators.

Can Astra use these data to file for emergency use authorisation in the US?

The situation in the US is much less clear. The FDA seems unlikely to accept data from studies that do not include any US patients as the basis for an emergency use authorisation, especially following the strong results with Pfizer/Biontech's BNT162b2 and Moderna's mRNA-1273.

Mr Pangalos was cagey about AZD1222's chances in the US, admitting that a scenario in which AZD1222 was available worldwide but not yet approved in the US was "possible".

One complication is that the group's phase III US study does not currently include the half-dose/full-dose regimen. This is something that Astra hopes to remedy by adding a new cohort to the trial "within weeks", Mr Pangalos said.

The company will need to move fast here, especially if BNT162b2 and/or mRNA-1273 are authorised soon, as people might not want to run the risk of getting a placebo in a clinical trial once marketed vaccines are available. Pfizer and Biontech submitted an EUA request on Friday.

Mr Pangalos told the media briefing that Astra would start talking to the FDA this week: this will initially involve sharing the latest data and firming up plans for the US pivotal trial, and then "interacting with them about the potential for submission or not".

Astra will face a delay if it is has to wait for US data. The company was forced to put its phase III programme on hold after a serious adverse event in the UK trial, thought to be transverse myelitis. The US study only restarted in late October. Around 10,500 US participants have now been dosed, Mr Pangalos said today; the target recruitment is around 40,000, up from 30,000 previously.

For his part, Leerink's Mr Porges believes that AZD1222 "will never be licensed in the US".

What about safety?

Astra was not giving much away today about safety, saying only that no serious adverse events related to the vaccine had been confirmed. Given the trial pause, this comment is unlikely to satisfy those who remain sceptical about the project's safety profile.

During the call, Mr Pangalos said that both dosing regimens had been well tolerated, with the main adverse events being things like sore arms, headache and fatigue. Safety looks set to remain a big focus when the full data are published.

How did AZD1222 perform in older patients?

It is also unclear how AZD1222 performed in older adults; the investigators have not had a chance to crunch these numbers yet. Generating an immune response here has long been a concern with Covid-19 vaccines because immune function declines with age.

However, even when full data are available they might not provide a comprehensive answer: only around 20% of participants in the UK and Brazil trials are over the age of 55, Mr Pangalos said.

Astra was keen, once again, to talk up the relatively simple storage requirements for AZD1222, as well as its manufacturing capabilities – the company has the capacity to make around three billion doses in 2021.

However, if the vaccine cannot get the go-ahead in the US it might come to be seen as a second-best option.

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