Evaluate Vantage

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US panel puts the spotlight on pivotal Covid vaccine readouts

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Moderna battles Pfizer/Biontech to generate the first pivotal study data for a Covid-19 vaccine.

Yesterday's US FDA advisory panel largely aimed to provide reassurance that no corners would be cut in getting a Covid-19 vaccine to market, but that fast approval was possible for vaccines that met robust criteria. Attention now falls on the timing of pivotal study readouts.

With Astrazeneca and Johnson & Johnson still on US clinical hold this looks like a two-horse race between Moderna's mRNA-1273 and Biontech/Pfizer's BNT162b2. The former revealed the completion of enrolment of a target 30,000 subjects yesterday, but the latter is not far behind.

While Moderna expects to have interim efficacy data by the end of November, Pfizer's chief executive, Albert Bourla, has said in an open letter that "we may know whether or not our vaccine is effective by the end of October". Both companies are targeting US emergency use authorisation, but they have to wait for sufficient safety findings to accrue first.

The FDA wants half the pivotal study participants to have generated two months of safety data before a filing can be made, and the stated timeline for this is the third week of November for Pfizer/Biontech, and December for Moderna.

Interims key

Unusually, protocols have been made available for most of the vaccines in pivotal trials. These reveal that BNT162b2 has more interim analyses than mRNA-1273, for instance, something that could give Pfizer/Biontech an earlier shot at seeing initial efficacy than Moderna, despite being slightly further behind in target enrolment.

Of course it is an entirely separate question what efficacy threshold would need to be met to secure an EUA, but the early interim analyses have relatively high bars for success.

The first interim analysis for BNT162b2 will be triggered after 32 Covid-19 cases have been recorded (20% of the total needed for final analysis), but for efficacy to be demonstrated a 77% effect versus placebo must be shown. Moderna wants to see at least 74% efficacy after 53 events trigger its first interim assessment.

It should also be stressed that, while in general all the pivotal trials measure Covid-19 cases in placebo

recipients versus subjects who get an investigational vaccine, how a positive case is defined varies from one study to another.

Covid-19 vaccines in western phase III trials					
Company	Biontech/Pfizer	Moderna	Astrazeneca	Johnson & Johnson	Novavax
Project	BNT162b2	mRNA-1273	AZD1222	Ad26.COV2-S	NVX-CoV2373
Description	mRNA (2 dose)	mRNA (2 dose)	Chimp adeno (2 dose)	Adeno type 26 (1 dose)	Recomb protein (2 dose)
Trial	NCT04368728	Cove	NCT04516746 (US); NCT04400838 (UK); NCT04536051 (Brazil)	Ensemble	NCT04583995 (UK)
Recruitment status	39,862 of planned 44,000 subjects enrolled*	Enrolment of 30,000 subjects completed**	30,000-subject US trial halted Sep 2020	60,000-subject US trial halted Oct 2020	9,000-subject UK trial started Sep 2020***
Efficacy measure	Covid-19 confirmed ≥7 days after last dose	Covid-19 defined as 2 systemic symptoms or 1 respiratory symptom, and positive by PCR, 14 days after second dose	Covid-19, positive by PCR, ≥15 days after second dose	Covid-19 (1 respiratory & 2 systemic symptoms for moderate) or (1 clinical sign for severe cases) and positive by PCR, ≥14 days after vaccination	Symptomatic Covid-19, positive by PCR, ≥7 days after second vaccination
Events for interim analyses & efficacy target	32 (77% efficacy) 62 (68% efficacy) 92 (63% efficacy) 120 (59% efficacy)	53 (74% efficacy) 106 (57% efficacy)	75 (70% efficacy)	20	66 (75% efficacy) 110 (59% efficacy)
Events for final analysis & efficacy target	164 (52% efficacy)	151 (50% efficacy)	150 (60% efficacy)	154 (60% efficacy)	152 (51% efficacy)
Data due	By end Oct (interim)	Nov (interim)	Year end (UK/Brazil only)	Unknown	Q1 2021
Trial protocol released?	Yes	Yes	Yes	Yes	Yes (redacted)
*Notes: *as at 19 Oct, with 34,601 receiving 2nd dose; **as at 22 Oct, with over 25,650 receiving 2nd dose; ***30,000-subject US trial has yet to begin. Source: trial protocols & company statements.*					

Jefferies analysts yesterday spelled out the importance of varying efficacy hurdles. They estimated that the ongoing UK trial of Astrazeneca's AZD1222 could yield data in mid-November if it shows at least 60% efficacy, but if the effect size is 50% the data would not come until the following month.

Interim analyses are blinded, so that if an efficacy bar is missed the trial continues unchanged, with no data revealed. Evercore ISI's Josh Schimmer has argued that, while consensus seems to be that Covid-19 vaccines will show around 70% efficacy, it is not unrealistic to expect something closer to 95%.

Either way, in Astra’s case it is doubtful whether a UK study could be used to back a US filing, especially as AZD1222’s US pivotal study remains on hold.

This was triggered after a case of transverse myelitis in the UK trial, and separately a death occurred in AZD1222’s Brazil study, though the latter has been determined not to be related to the vaccine. Meanwhile, J&J’s Ad26.COV2-S is on hold after an “unexplained illness”.

With development proceeding at pace falling behind becomes a big problem; for instance, can integrity of a placebo cohort in a controlled pivotal trial be maintained once a vaccine is available under EUA? Going into yesterday’s US panel Pfizer and J&J expressed concerns over this, but the view was maintained that studies had to continue unaltered for their results to hold statistical rigor.

Overall, while nothing new was revealed in terms of clinical data, the FDA largely underlined its firm stance on vaccine review standards. We should soon see this stance tested.

This story was updated to reflect Novavax's subsequent revalation of a redacted version of its UK phase III plan.