Evaluate Vantage

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J&J and Novavax push Covid-19 vaccine candidates into late-stage testing

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Five candidates are now in phase III trials in the West, as Pfizer approaches its first interim readout.

The race to bring a Covid-19 vaccine to market has heated up again with the entry of two more candidates into phase III this week: Johnson & Johnson's Ad26.COV2-S (now known as JNJ-78436735), and Novavax's NVX-CoV2373.

And, with four out of the five late-stage contenders now having published their trial protocols, it is becoming clearer what each vaccine will need to show. First to report should be Biontech and Pfizer's BNT162b2, with initial data expected by the end of October – but results might come even sooner than that.

One analytics firm, Airfinity, has calculated that the first interim analysis of the vaccine's phase III study, which will be triggered after 32 events, could come as early as September 27.

Moderna is not far behind – the group has said that the first results with its vaccine, mRNA-1273, should be available by November.

The FDA has requested a median of at least two months' safety observations on trial participants as part of any application for emergency use, Leerink analysts wrote recently. This might put paid to any hope of a vaccine becoming available before the US election in November.

One shot

Johnson & Johnson's JNJ-78436735, which went into a 60,000-patient pivotal trial this week, might have a logistical edge over the other late-stage vaccines in that it only requires one injection. J&J is also planning a UK trial of a two-dose schedule.

Furthermore, JNJ-78436735 incorporates a tried-and-tested technology – it uses the same adenovirus as part of J&J's Ebola vaccine regimen, which received EU approval in July.

Novavax, too, is testing a familiar approach: its NVX-CoV2373 is a recombinant protein vaccine, a type in widespread use today. The next most advanced recombinant protein Covid-19 candidate, from Sanofi and Glaxosmithkline, is not expected to start pivotal testing until December.

NVX-CoV2373 also looks the most convenient in terms of storage requirements: it can be kept at 2-8°C. JNJ-

78436735 is stable for two years at -20°C and “at least three months” at 2-8°C. The storage requirements of the mRNA candidates are much more onerous.

Per protocols

All of the phase III contenders bar Novavax have now published their trial protocols – and Novavax has said it will do the same “in the coming days” for its 10,000-patient UK pivotal trial, which it announced yesterday.

This has given investors a unique chance to peer into the workings of these studies. But differences, particularly in the way Covid-19 infection is defined, will make cross-trial comparisons even trickier than usual when the data do emerge.

For example, only J&J is evaluating moderate-to-severe disease as its primary endpoint – the other developers also include mild disease. Meanwhile, the Novavax study has two co-primary endpoints, one looking at moderate-to-severe disease, and the other evaluating any symptomatic Covid-19 infection.

The way Covid-19 is defined also varies. Pfizer’s trial has the least stringent definition, with patients only having to report one of a list of symptoms. Moderna, Astra and J&J’s studies require one major symptom such as difficulty breathing, or two symptoms such as chills and headache.

Another big difference is the number of events needed for the first interim analysis. Astra is the strictest here, requiring 75 events to trigger its first look. This might give greater confidence in its interim analysis, according to Leerink, as the higher bar means the interim data are likely to be more similar to the primary endpoint analysis than in trials whose interim cut will come earlier.

Astra uncertainties

However, recruitment into the US trial of Astrazeneca's AZD1222 has not yet restarted following a halt caused by a case of transverse myelitis in the UK; curiously, the UK study has resumed, as well as trials in Brazil and Africa.

Astra’s head of biopharmaceuticals R&D, Sir Mene Pangalos, recently told Leerink analysts that the company should have interim data from its UK and Brazil phase III trials by the end of this year; however, it is unclear whether the FDA would even consider reviewing the package if the US data are still immature.

According to Leerink, Astra is in the final stages of submitting documents to the FDA and hopes to resume the study soon after. By that time, the agency might have its hands full with the first mRNA vaccine data.

Covid-19 vaccines in western phase III trials					
Company	**Biontech/Pfizer**	**Moderna/NIAID**	**Astrazeneca/Uni of Oxford**	**Johnson & Johnson**	**Novavax**
Project	BNT162b2	mRNA-1273	AZD1222	Ad26.COV2-S/ JNJ-78436735	NVX-CoV2373
Description	mRNA vaccine	mRNA vaccine	Chimp adenovirus vaccine	Adenovirus type 26 vaccine	Recombinant protein vaccine
Phase III trial ID	NCT04368728	Cove (NCT04470427)	NCT04516746 (US ph3); NCT04400838 (UK ph2/3); NCT04536051 (Brazil ph3)	Ensemble (NCT04505722)	EduraCT: 2020-004123-16
Recruitment target	44,000	30,000	30,000 (US trial)	60,000	10,000 (UK trial)
Recruitment status	29,012* pts recruited	25,976** pts recruited	US trial not yet restarted; UK & Brazil trials resumed	Started Sep 2020	Started Sep 2020
Efficacy target	60%	60%	50%	60%	60%
No. of events at completion	164	151	150	154	N/A
No. of events at first interim analysis	32	53	75	20	N/A
Data due	By end Oct	By end Nov	By year end (UK/Brazil only)	Ph1/2 data preprint posted	Unknown
Trial protocol released?	Yes	Yes	Yes	Yes	Due "in coming days"
Deep freezing required	Yes	Yes	Yes	No	No

**As of Sep 15, 2020; **As of Sep 18, 2020. Source: Eric Topol on Twitter; clinicaltrials.gov; trial protocols.*

This story has been updated to include a link to J&J's ph1/2 preprint data, and the Novavax ph3 study's EduraCT number.