

The big Covid-19 trials still to report



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New findings for IL-6 blockade in the Recovery trial finally confirm a signal. Can pending pandemic readouts for other mechanisms do the same?

The anti-IL-6 antibodies were among the first drugs doctors reached for when Covid-19 emerged, but the failure of several trials to establish a clear benefit meant questions around their use lingered. However, last week a 4,000-patient arm of the Recovery trial found a clear mortality benefit in severely ill hospitalised patients for Roche's Actemra, at least when combined with the steroid dexamethasone.

The Recovery researchers believe that it was study size – previous trials had been much smaller – that allowed a robust finding to emerge. *Evaluate Vantage* has scoured clinical trials records for other large Covid-19 studies that have yet to report, and from which reliable signals might yet be seen.

Few of these are as big as Recovery, run in hospitals across the UK. It should be noted that most patients in the Actemra and standard-of-care cohorts were also on dexamethasone, which has separately been [shown to have a mortality benefit](#). In Recovery no benefit was seen for Actemra without dexamethasone versus standard of care without the steroid, though this subgroup was small.

The main finding of this latest Recovery readout was [a 14% reduction in 28-day mortality](#) for patients treated with Actemra, which Roche markets for rheumatoid arthritis and contains the active ingredient tocilizumab; the risk of progressing to a ventilator was also significantly reduced. To be included in the trial subjects had to have low blood oxygen and high markers of inflammation.

Professor Richard Haynes, one of Recovery's leaders, told *Evaluate Vantage* that he did not believe that these selection criteria were key to the different outcome in Recovery versus previous failed trials of Actemra in Covid-19. It was more that other studies were just too small to determine the treatment effect reliably.

What this means for another anti-IL-6 MAb, Sanofi and Regeneron's Kevzara, which contains the active ingredient sarilumab, is unclear. [Two trials failed to find any signal](#) last year, although the data have yet to be published outside of a press release.

It will be interesting to see if researchers can salvage anything from the data, in light of the Recovery finding. Regeneron told *Evaluate Vantage* that next steps for sarilumab's Covid-19 programme had not been determined.

The table below highlights some large clinical trials of other projects that have yet to demonstrate a conclusive benefit in Covid-19, and that should yield data in the coming months. A notable omission is the large clinical programme of [Astrazeneca's MAb AZD7442](#), results on which are due in the coming weeks.

Bigger is better? Some of the largest Covid-19 trials to watch

Trial (sponsor)	Enrolment	Project (company)	Description	Readouts
Activ-3 (NIAID)	10,000	AZD7442 (Astrazeneca); VIR-7831/GSK4182136 (Vir/Glaxosmithkline); BR11-196 & BR11-198 (Brii)	Basket trial in hospitalised patients	Further futility readouts expected Feb
ACTCOVID19 (Canadian academic group)	4,000	Colchicine; interferon-beta; aspirin; Xarelto (Bayer)	Basket trial in hospitalised and outpatients	Results due 2021
Cobra (Canadian academic group)	3,626	BCG vaccine	Prevention and reduction of Covid-19 infection	Results due 2021
MK-4482-001 and 002	3,150	Molnupiravir (Ridgeback/Merck & Co)	Hospitalised and non-hospitalised patients	Results due Q1 2021
Activ-2 (NIAID)	2,000	SNG001 (Synairgen); AZD7442 (Astrazeneca); camostat mesilate (Sagent Pharmaceuticals)	Basket trial in outpatients	Results due 2021
Cov-immuno (Canadian academic group)	1,500	IMM-101 (Immodulon Therapeutics)	Reducing the risk of severe infections in cancer patients	Results due late 2021/2022
NCT04590586 (Amgen)	1,400	Otezla (Amgen); Takhzyro (Takeda); Zilcoplan (UCB)	Time to recovery in hospitalised patients	Results due late 2021/2022
Stop Covid 2 (US academic group)	1,100	Fluvoxamine (generic)	Early treatment to prevent disease progression	Results due late 2021
NCT04602000 (Celltrion)	1,020	CT-P59/regdanvimab	Disease progression in mild to moderate patients	Results due 2021
Mir-Age (Abivax)	1,034	ABX464	Prevention of acute respiratory failure	Results due Q2 2021
NCT04734873 (Corvus)	1,000	CPI-006	Disease progression in hospitalised patients	Results due 2022
Oscar (Glaxosmithkline)	800	Otilimab	Prevention of death in severe patients	Results due H1 2021
NCT04382924 (Algeron)	682	NP-120/ifenprodil	Prevention of severe disease in hospitalised patients	Results due Feb 2021
Sprinter (Synairgen)	610	SNG001	Disease progression in hospitalised patients	Results due 2021

Sources: EvaluatePharma, clinicaltrials.gov & company statements. Note: list not intended to be exhaustive.

This shows that a mixed bag of approaches have made it into some substantial clinical endeavours. It is notable that, like Recovery, some of the biggest undertakings are being funded by government-backed academic groups. So, even if commercially sponsored smaller trials yield signals of efficacy, it could well come down to the taxpayer to confirm a use.

The NIAID-backed Activ programme looks is set to remain a useful testing ground for hopeful mechanisms.

Interestingly, camostat recently joined the Activ-2 trial. The generically available serine protease inhibitor has been widely studied by various academic groups around the world, and its inclusion in this study suggests that some convincing signals have been seen.

Some studies look more likely to yield useful readouts than others. For example, several are ongoing globally to investigate the role of BCG vaccination in reducing the risk of Covid-19 infection, though the swift rollout of pandemic vaccines has surely negated the usefulness of any encouraging findings that might emerge.

Arguably leftfield approaches include Algernon's NMDA receptor antagonist ifenprodil, which the company believes could help decrease inflammation by reducing the infiltration of neutrophils and T cells into the lungs. Another large academic group is investigating the use of the generic antidepressant fluvoxamine - better known as Luvox - as a treatment for mild Covid-19 patients.

Glaxo's otlimab is the leading anti-GM-CSF antibody, several of which are being tested in Covid-19. These target another pro-inflammatory cytokine and the experience with anti-IL-6 MAb suggests that finding a benefit in targeting GM-CSF might not be straightforward.

And two tiny biotechs, France's Abivax and the UK's Synairgen, have come a long way with their respective projects. Results due soon from both should show whether they can make a splash; the former's ABX464 is said to have both antiviral and anti-inflammatory properties, while the latter's SNG001 is an inhaled formulation of interferon beta-1a.

The project with highest hopes attached, however, is probably Merck's antiviral molnupiravir, which is in two extensive pivotal studies that should read out in the next couple of weeks. After the company's vaccine disappointment, the big pharma wants to find a role to play in the pandemic at last.

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