Evaluate Vantage

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Toxicity concerns now hit the Covid antibody approach

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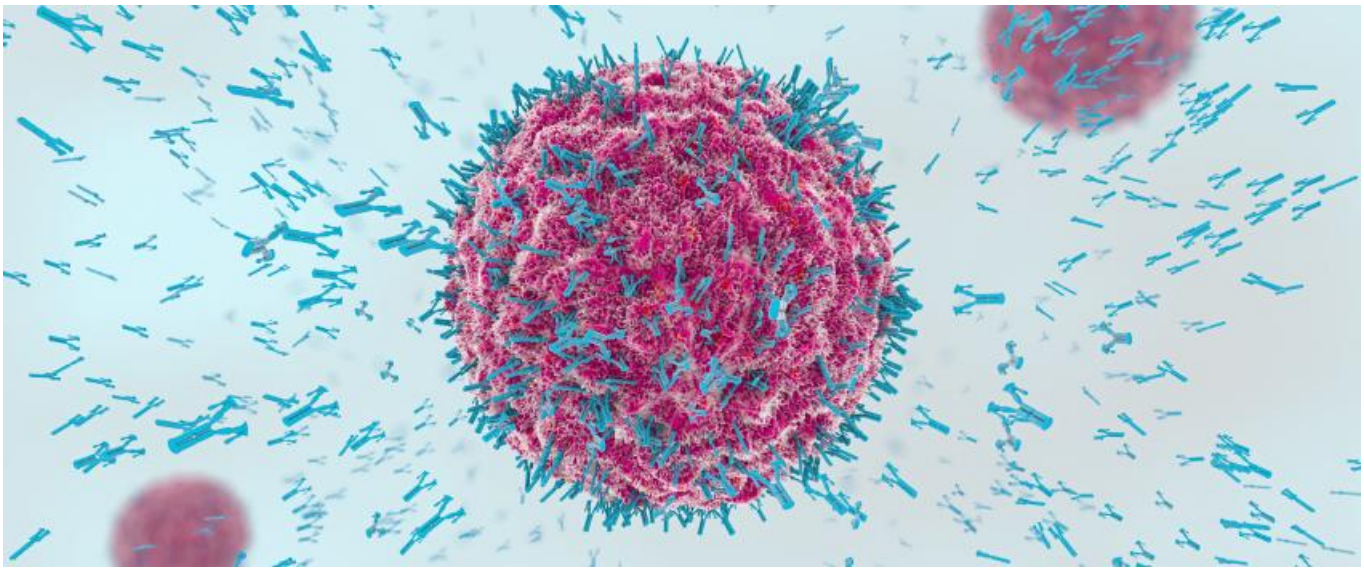


An NIAID-sponsored study of a Lilly antibody has been paused for possible toxicity, prompting speculation over the cause of the problem.

Yesterday's revelation of yet another Covid-19 clinical trial halt – this time for Lilly's antibody LY3819253 – will trigger speculation as to what has caused a problem while other molecules have presented relatively clean profiles.

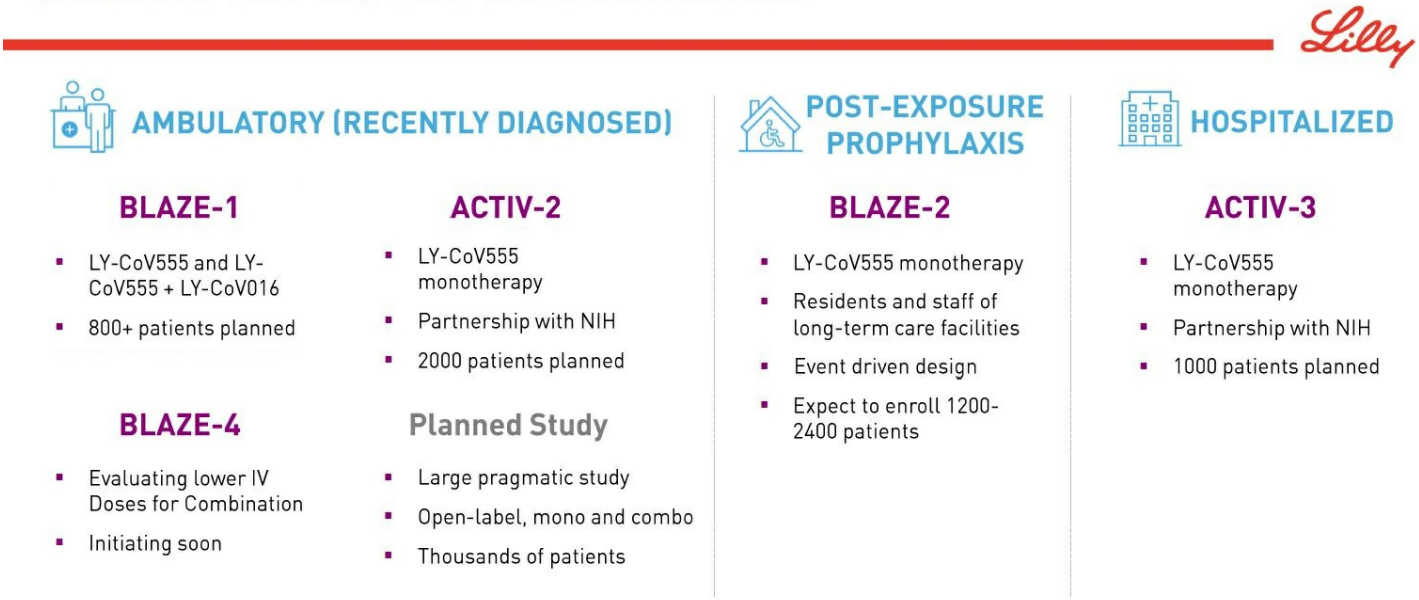
Until more is revealed, however, the likeliest explanation is patient heterogeneity in the trial in question, as well as the fact that other studies have concerned very different populations. Still, it is worth noting that the most advanced players have taken differing approaches to developing an antibody against Covid-19.

While much remains undisclosed about the precise constructs in development, preclinical papers shed some light. One obvious difference between the antibodies is that some contain modifications in their tail, the so-called Fc region, but others do not.

A natural antibody's Fc region does not bind the desired antigen, but rather interacts with receptors to activate the immune system to recruit T cells and release cytotoxic molecules. Some engineered MAbs have modified Fc regions to increase or decrease their half-lives, or to modulate the immune response.

LY3819253, the Lilly MAb whose Activ-3 study has been halted, is a full antibody, with an unmodified Fc region. One line of speculation, therefore, could be whether its influence on the immune system might have contributed to deleterious effects.

However, it is far too early for this sort of conjecture. All that is known is that the US NIAID-sponsored study was halted after a recommendation from its safety monitoring board; after enrolling 326 out of a planned 1,000 subjects an imbalance in clinical status was seen between LY3819253 and placebo recipients, but nothing is known about the nature of this.



The Activ-3 trial has been halted; the rest of the studies are unaffected. Source: Lilly presentation.

Importantly, however, Activ-3 recruits patients who have been hospitalised for acute medical care. Other studies to yield data, including LY3819253's the Blaze-1 trial and a test of Regeneron's REGN-COV2 combo, have all concerned mild Covid-19; Lilly speculates that patients with the severest symptoms might not benefit from an antibody, and notes that antivirals might be in play too.

LY3819253 is separately being studied in combination with another Lilly MAb, LY3832479. Interestingly, the latter is Fc-null, meaning that it elicits no Fc-mediated effects, exerting its activity solely by competitively blocking the receptor-binding domain on Covid-19.

Meanwhile, REGN-COV2 comprises two MAbs that both have fully functioning Fc regions, and its safety profile has not raised concerns, albeit in non-hospitalised patients.

Indeed, a preclinical study compared the full versions of these MAbs against just their antigen-binding fragments, and the former exhibited better activity than the latter. This led the authors to state that bivalent binding (meaning to the desired antigen and via the Fc region) to cause cross-linking might augment efficacy.

Another combo, another approach

Those interested in antibody design will note that a separate combo, Astrazeneca's AZD7442, which last week entered phase III, is made up of two MAbs that both have modified Fc regions to increase half life but reduce Fc binding.

No doubt speculation as to which approach is best and safest will continue. All that seems apparent for now is that, no matter how much pressure developers are under to bring the coronavirus pandemic under control fast, a system exists to ensure that no safety corners are cut.

This has tripped up two Covid-19 vaccines, and now an antibody, but it should not necessarily be bad news.

Selected clinical-stage anti-Covid-19 antibodies (all fully human, IgG type)			
Project	**Alternative name**	**Target**	**Modifications?**
Regeneron			
REGN10987	REGN-87	RBD epitope cluster 1	Full antibody
REGN10933	REGN-33	RBD epitope cluster 2	Full antibody
Lilly			
LY3819253	LY-CoV555/ bamlanivimab	RBD	Full antibody
LY3832479	LY-CoV016	RBD (separate epitope)	Fc-null
Vir/Glaxosmithkline			
VIR-7831	GSK4182136	Based on S309 antibody isolated from memory B cells of a Sars survivor	Engineered with "LS" mutation in Fc region to increase lung tissue bioavailability and extend half-life
Astrazeneca			
AZD8895	–	Derived from convalescent plasma after Covid-19 infection	Optimised with half-life extension and reduced Fc binding
AZD1061	–	Derived from convalescent plasma after Covid-19 infection	Optimised with half-life extension and reduced Fc binding
Note: Regeneron calls the REGN10987 + REGN10933 combo REGN-COV2; Astrazeneca calls the AZD8895 + AZD1061 combo AZD7442. RBD=receptor binding domain. Source: scientific papers and company statements.			