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Managing the Covid-19 Pandemic: Therapeutics Are as Important as Vaccines

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US President Donald J. Trump received Regeneron's REGN-CoV – an antibody cocktail – when he was hospitalised with Covid-19. After Trump declared he had been "cured" (there is currently no confirmed cure for Covid-19), the company saw increased demand and its stock price rose. The American president was treated with REGN-CoV under a compassionate use authorisation, and the company has now applied to the US regulator, the Food & Drug Administration (FDA), for an Emergency Use Authorisation (EUA). To be clear, REGN-CoV is yet to have clinical proof of efficacy against Covid-19; it is, however a treatment that has shown promise in early clinical development. The global attention on REGN-CoV, remdesivir and dexamethasone – which President Trump also received as part of the treatment regimen – have once again highlighted the role of therapeutics as powerful tools to treat Covid-19, both in terms of reducing symptoms and halting the infection itself.

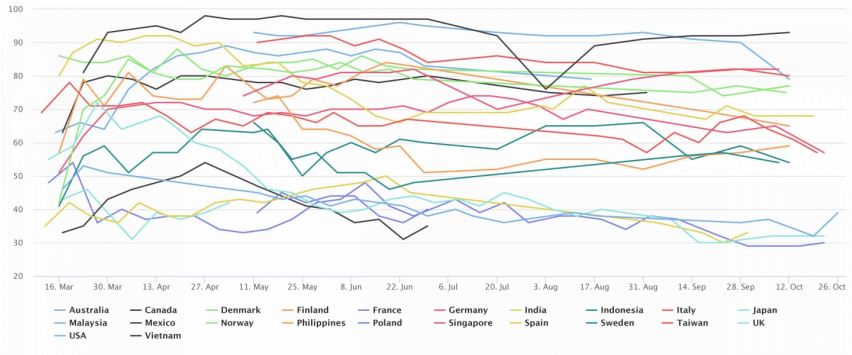
Therapeutics, as we argued in our earlier paper "Therapeutics and Politics: The Evolving Covid-19 Landscape", "will prevent health-care systems from being overloaded, keep people off ventilators, shorten hospital stays, and allow those who are infected to remain healthy and able to live their lives, including returning to work. These are critical for economic recovery to occur. Moreover, there is some evidence derived from early clinical trials that if administered early during the infection, some treatments may halt the progression of the disease. Robust, late-stage clinical trials will be necessary to establish this. If proved true, this would most certainly be a game-changer and provide a bridge to vaccines, if not a complement. Given the fact that many treatments in clinical development are off-label drugs, it is likely that an effective treatment will be available to the general public before a vaccine."

The political context, the spike in infections, new lockdowns, restrictive measures and emerging cases of "Long Covid" all give urgency to the need to distribute antibodies sooner rather than later. Because any approved vaccine(s) will work only before a person contracts the disease, antibodies in particular are likely to be central to managing the pandemic. Their performance in clinical trials suggests that these treatments have a crucial role to play. Antibodies could benefit those who are severely ill with Covid-19 and are most vulnerable to contracting the disease. Some antibodies may be more effective at a certain stage of illness than others. We understand that clear answers about the extent that antibodies work, how long they are effective, and which work best for various groups will be more robust when delivered through randomised controlled trials. The UK's RECOVERY Trial provides such a vehicle, but not enough people are enrolled. More people should be allowed to join the trial, shifting eligibility to include those outside of hospital settings who become infected and are at risk. Expanding the trial would provide life-saving antibodies to those who need them, rather than the low number who currently receive them. The streamlined process that the trial currently uses to review data and make decisions is critical to ensuring that promising drugs move through clinical development expeditiously. Moreover, such efforts must be supported by ramped up production, as the nature of the manufacturing process is more complex than that for many vaccines under clinical development. Existing bioreactor capacity that can be reprioritised to produce antibodies should be used given the current limited supply of antibodies.

The Politics–Covid Treatment Nexus

There have been a number of important developments in the therapeutics landscape since the publication of our last paper. The argument that therapeutics will be crucial in managing the pandemic still holds, yet the political context has evolved along with our fund of knowledge with respect to therapeutics. For the UK, as well as other rich countries, there is a dilemma: Covid-19 cases are rising sharply, as dire predictions by public health experts who warned of an autumn wave seem to be coming to pass. The number of cases has surpassed the earlier peak in September and new restrictions have been introduced (a tiered system for England is set to be followed up with a lockdown beginning on 5 November); as of 14 October, the UK had 650,000 cases. [1] The virus has bedevilled even countries whose governments have implemented robust testing and tracing systems, such as Germany, which saw a 60 per cent increase in new infections over a two-day period between 7 and 9 October. [2] A frustrated, anxious public is losing confidence in governments' capability to effectively manage the pandemic, resulting in uneven adherence with restrictions at a time when compliance is critical and can spell the difference between life and death, good health and severe illness. YouGov has documented this ebb and flow of public confidence and the data show that governments in France, the US, and UK rate the lowest, while many governments face an overall decline in public confidence (see Figure 1). [3] While this is all quite dispiriting news, it is not the entire story.

Figure 1 – How do citizens perceive their government's handling of the pandemic?



Source: YouGov

As we outline in our forthcoming paper on vaccines, pharmaceutical companies are closer to efficacy results that will determine the final approval and registration of a vaccine, despite pauses in a few phase III clinical trials. [4] While it is becoming increasingly clear that no vaccine will be a silver bullet, a vaccine will assist governments in pandemic management. Progress has been made with quality of diagnostic tests, which have improved dramatically and can be administered at point of use and are faster and more accurate than earlier ones. Finally, medical professionals have learned about how the disease acts and are

more effective at treating people. The treatment landscape has evolved significantly over the past few months, with antibody-based treatments showing particular promise in clinical trials.

Status of Treatments in Clinical Trials: What Have We Learned?

Dexamethasone is the first coronavirus treatment proven to reduce the risk of death. Several other drugs have achieved emergency use authorisation in various countries where they have shown enough promise in clinical development to receive that designation. The gold standard, however, entails successful completion of phase III clinical trials.

It has taken some time to generate conclusive evidence from drugs undergoing clinical trials. Part of this is due to the lack of coordination and the nature of these trials. This has been the challenge in the US in particular, which suffers from a fragmented health system that is difficult to coordinate, as well as lack of a clear strategy from the government. In contrast, the UK has benefited from the structure of its National Health Service (NHS), which provides the basis for large patient clinical trials that can be better structured and coordinated so as to generate clear and decisive findings to identify effective drugs and, as importantly, those that are ineffective.

An example of this is the RECOVERY Trial, the focus of which is "the impact of candidate treatments on mortality and on the need for hospitalisation or ventilation". [5] It is the world's largest trial of Covid-19 drugs and has more than 12,000 participants. Drugs currently being trialled include:

- Low-dose dexamethasone (now only recruiting children)
- Azithromycin (a commonly used antibiotic)
- Tocilizumab (an anti-inflammatory treatment given by injection)
- Convalescent plasma (collected from donors who have recovered from Covid-19 and which contains antibodies against the SARS-CoV-2 virus)
- REGN-COV2 (a combination of monoclonal antibodies directed against coronavirus) [6]

The RECOVERY Trial – which is trialling both existing and new drugs – provided clear evidence that dexamethasone reduced death in Covid-19 patients on ventilators by a third, and a fifth of those on oxygen. That trial began in March 2020 and was stopped on 8 June 2020 as a result of clear and overwhelming evidence of the steroid's effectiveness. [7] The RECOVERY Trial also provided proof that the much-hyped hydroxychloroquine was ineffective against Covid-19; lopinavir and ritonavir were also shown to be ineffective. [8] These findings have been validated in the World Health Organisation (WHO) Solidarity trial. [9] Knowing definitively what does not work is as valuable as knowing what does.

The antiviral remdesivir (which is made by Gilead), has been approved for emergency use authorisation in a number of countries; the US drug regulator recently gave it full approval. In the UK, the drug is

administered to selected Covid-19 patients in hospital settings. In the European Union, the drug received conditional marketing authorisation, and is "indicated for the treatment of Covid-19 in adults and adolescents (aged 12 years and older and weighing at least 40kg), with pneumonia requiring supplemental oxygen … A conditional marketing authorisation in Europe is initially valid for one year but can be extended or converted into an unconditional marketing authorisation after the submission and assessment of additional confirmatory data." [10] It is approved to treat Covid-19 patients in Japan, Canada, the Czech Republic and a number of other countries. The US FDA just announced full approval of remdesivir to treat hospitalised patients. [11]

However, the WHO's Solidarity trial just released the non-peer-reviewed results of its phase III clinical trial of remdesivir. It was trialled in more than 11,000 patients; clear evidence indicates that remdesivir (along with lopinavir, interferon and hydroxychloroquine) has no effect on either a Covid-19 patient's chance of survival or of the need to use a ventilator. [12] Moreover, there was no effect on the length of a hospital stay. Not surprisingly, Gilead disputes the results.

What has emerged from the wide range of trials under way globally is that three approaches hold promise when it comes to treating Covid-19:

- Antiviral drugs that directly inhibit the coronavirus's ability to replicate, thereby keeping the viral load low and undetectable. (The WHO Solidarity trial does not support this, raising questions about the other trial for remdesivir.)
- Drugs that keep the immune system from overreacting in ways that cause damage to the body. This is not uncommon in patients with severe cases of Covid-19.
- Antibodies that can target the virus, either made synthetically or harvested from survivors' blood plasma or made in a lab. [13]

Different drugs can be more effective at different phases of Covid-19. Antivirals may work better at the beginning and immune-response modulating drugs later if the disease worsens. [14]

Table 1 lists the drugs that are under clinical development, according to regulatory authority professionals. Several have emerged that appear to hold particular promise as a bridge to a vaccine. Two of the three drug makers have already applied to the FDA for emergency use authorisation, with the expectation that regulators in other countries also will grant such approval. Several are worth highlighting based on preliminary results. AstraZeneca – which also has a leading vaccine candidate in Phase III clinical trials (currently paused in the US) – has an entrant in the therapeutics category: Calquence (acalabrutinib). "In the US, Australia, the United Arab Emirates, and India, Calquence is approved for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL), and in Canada for CLL. Calquence is also approved in the US and a few other countries for adult patients with mantle cell lymphoma (MCL) who have received at least one prior

therapy." [15] Calquence has shown promising results in early trials. The drug was assessed in a sample size of 19 people hospitalised with Covid-19 and who were experiencing severe inflammation and/or hypoxia; all but four were on either ventilators or high-flow oxygen. "The oxygenation and clinical status of most patients on supplemental oxygen improved relatively rapidly following acalabrutinib initiation, which was temporally associated with a normalisation of inflammatory markers. Also, while patients on mechanical ventilation had a more variable clinical response to the drug, improved oxygenation in half of these patients allowed them to be extubated." [16] This drug falls into the category of those that quiet the body's immune system. It is of particular potential value given its results in allowing patients to be removed from ventilators, which is associated with high rates of mortality.

Antibody Treatments for Covid-19: Status of Clinical Development

There are essentially three types of antibody-based treatments: single monoclonals; cocktails of monoclonals (which is the focus for most Covid-19 products); and polyclonals, such as plasma therapy. The emerging evidence about them suggests that they can be particularly effective in treating or preventing Covid-19. One of the ways the human body protects itself against bacterial and viral infections is through the production of antibodies that bind to the micro-organisms, preventing and clearing the infection. Antibodies can be drawn from many sources. Scientists can either harvest antibodies from the blood of people who have recovered from an infection. This is the origin of convalescent plasma that is the basis for some of the Covid-19 treatments under clinical development. Scientists can also make antibodies synthetically and use them to bind to bacteria and viruses and render them ineffective. Antibodies can be used to calm the body's immune system down to prevent overreaction that causes damage to the body. This is called the "cytokine storm", which has proved fatal for many Covid-19 sufferers.

Antibody-based treatments can be a powerful tool in the arsenal to fight infectious-disease outbreaks, both before and even if vaccines eventually make it to registration and widespread use. They show enormous potential as both a way to prevent Covid-19 infection if administered either early in the course of the infection, or before exposure to the virus, especially in high-risk populations. They also may be effective as a therapy for people who become sick. As such, they can serve as a bridge to a vaccine with a role to play to complement immunisation campaigns. Table 2 shows the monoclonal antibodies that are under clinical development.

Several companies and one multi-stakeholder partnership with candidates in the antibodies category are worth highlighting; except for the partnership, the companies highlighted are in phase II or III clinical trials. The first is Lilly, which is trialling LY-CoV555 (which will be known as bamlanivimab and is part of the US Operation Warp Speed programme) and LY-CoV016 (which will be known as etesevimab). In a phase II trial that enrolled 450 patients in an outpatient setting, one of the three doses of LY-CoV555 administered was successful in reducing the amount of SARS-COV-2 present in patients after 11 days, showing that the drug has an antiviral effect that can reduce Covid-19-related hospitalisation for mild to moderate cases. "Additional analyses of viral data demonstrated that LY-CoV555 improved viral clearance at an earlier time point (day three) and reduced the proportion of patients with persistently high viral load at later time points." [17] Part of the phase III trial evaluated 326 participants who have been hospitalised with mild to moderate Covid-19. [18] Lilly announced on 26 October that results indicated that LY-CoV555 is not effective in treating hospitalised patients. [19]Another component of the phase III trial evaluates the same participants with mild to moderate Covid-19 who are not in the hospital. Finally,

LY-CoV555 is also being tested as a preventative therapy for residents of nursing homes and employees who may have been exposed to the virus.

Positive results could position the treatment as a powerful prophylactic for the most vulnerable – the elderly, frontline health workers, and people with underlying conditions and diseases. Lilly partnered with AbCellera, which initially identified the antibody that Lilly later trialled and is expected to have 100,000 doses ready later this month. The company is in discussions with global regulators following the positive results. There was, understandably, concern about the pause in the clinical trial as a result of an unspecified safety issue that emerged in the antibody-treated group, which showed a different "clinical status" after five days of treatment compared to the group receiving the placebo. [20] A regulatory concern with respect to manufacturing of the antibody was raised by inadequate control over computer systems in the New York site where LY-CoV is made; the drug itself was not the problem. Lilly's LY-CoV016 is under development through a licensing deal with China's Junshi Biosciences and has launched a phase II trial testing both antibodies in patients with early, mild to moderate Covid-19. [21]

Second, US-based Regeneron's REGN-COV2 is an antibody cocktail (two separate antibodies are in it) that has been assessed in a multiphase clinical trial. [22] It has a proprietary breed of genetically engineered mice that make human antibodies when infected with lab-grown cells that resemble the SARS-CoV-2 shape. [23] Regeneron "combined its two most potent, non-competing, virus-neutralising antibodies into a single therapy in the belief it is necessary to attack the coronavirus from two angles to prevent the emergence of mutant drug-resistant forms of the pathogen." [24] Preliminary results are promising. "The first data from a descriptive analysis of a seamless phase I/II/III trial of its investigational antibody cocktail REGN-COV2 show[ed] it reduced viral load and the time to alleviate symptoms in non-hospitalised patients with Covid-19. REGN-COV2 also showed positive trends in reducing medical visits. The ongoing, randomised, double-blind trial measures the effect of adding REGN-COV2 to usual standard-of-care, compared to adding placebo to standard-of-care. This trial is part of a larger programme that also includes studies of REGN-COV2 for the treatment of hospitalised patients, and for prevention of infection in people who have been exposed to Covid-19 patients" [25] Initial analysis was based on the first 275 patients enrolled; a minimum of 1,300 patients will be involved in phase II/III trial and will be assessing non-hospitalised participants. [26] In addition, hospitalised Covid-19 patients are being studied in phase II/III trials. However, Regeneron recently paused enrolment in the trial of hospitalised intubated patients. Another component of the phase III trial evaluates the cocktail for the prevention of Covid-19 in household contacts of infected individuals. [27] The company has $450 million in support from the US government to develop its antibodies programme and is pursuing emergency use authorisation from the FDA. The Trump administration has stated publicly that it would make the drug available to patients in the US free of charge; it is not clear what specific plans there may be to implement this pledge. The US government has already purchased 300,000 doses.

Third, AstraZeneca's candidate, AZD7442, is a combination of two long-acting antibodies (LAAB) derived from convalescent patients after SARS-CoV-2 infection. The company licensed their antibodies from Vanderbilt University Medical School, which made the discovery. The phase III trial has multiple components: one will evaluate safety and efficacy to prevent infection for up to a year in 5,000 participants; one will evaluate post-exposure prophylaxis and pre-emptive treatment in 1,100 participants; another trial to evaluate treatment of Covid-19 is in the planning phase for about 4,000 people. [28] The synthetic drug combination is designed to remain effective for between 6 and 12 months after a single dose is administered and is expected to reduce the risk of resistance developed to the virus. [29] The longer period of effectiveness is because of AstraZeneca's half-life extension and reduced Fc receptor binding. Like Regeneron, AstraZeneca has received more than $450 million from the US government; the company will develop and supply 100,000 doses starting towards the end of 2020, with an option to supply up to 1 million doses in 2021. The UK will receive some doses from the company, but it is unclear how many will be available. [30] The UK government is in the market to secure antibody-based treatments from companies conducting clinical trials.

Both Regeneron and AstraZeneca have deployed a two-antibody approach, while Lilly has a single antibody drug. That decision was purposeful, with Lilly arguing that doing so makes it possible to manufacture double the amount of a combination of two antibodies, triple the amount of three antibodies, etc. Lilly has prioritised manufacturing capacity, but it could be at a disadvantage compared to Regeneron and AstraZeneca because the novel coronavirus could be more resistant to a single antibody as opposed to two. Lilly is making a bet that the drug's extremely high potency will remain effective. It has a mitigation strategy in place: if LY-CoV555 become less potent, then it has a second antibody that it can add to make a cocktail that it has access to through a partnership with Junshi BioSciences. [31]

Fourth, Takeda conceived and spearheaded the CoVIg-19 Plasma Alliance, a collaboration that includes plasma companies with the support of global organisations outside the industry, and has announced a phase III clinical trial of its anti-Covid-19 Hyperimmune Globulin (CoVig-19) medicine. [32] "The trial will evaluate the safety, tolerability and efficacy of an investigational anti-coronavirus hyperimmune intravenous immunoglobulin (H-Ig) medicine for treating hospitalised adults at risk for serious complications of Covid-19 disease. If successful, the Alliance's H-Ig may become one of the earliest treatment options for hospitalised Covid-19 patients." [33] The medicine requires the combining of convalescent plasma (CP) donations from multiple patients. Antibodies are purified and concentrated from convalescent patient plasma, generating a potent medicine that attacks the virus from multiple directions. Importantly, FDA-authorised CP requires blood-type matching, whereas hyperimmune globulin does not, which makes it allowable for all eligible patients. [34] The intravenous medicine will be administered to 500 patients in 18 countries who are at risk for serious complications from Covid-19; these are patients who do not show either end-organ failure or life-threatening organ dysfunction. It is

being administered in addition to remdesivir. Takeda's approach is different from other companies because it relies on plasma collected from patients who have recovered from Covid-19, making manufacturing a potential bottleneck. A study just published in the *British Medical Journal* found that CP is limited in its effectiveness and does not prevent either death or the progression of Covid-19. It is not likely to be the final word on the efficacy of CP for several reasons, ranging from the fact the study did not assess CP containing high levels of coronavirus antibodies to evidence from other studies that shows that administering plasma with high levels of antibodies to patients early in the course of the disease did reduce death rates. [35]

Fifth, South Korea's Celltrion recently announced the start of its phase III clinical trial of CT-P59, its monoclonal antibody treatment candidate that could be used to prevent illness from Covid-19. The beginning of the post-exposure prophylaxis clinical trial will enrol about 1,000 people who are contacts of people infected with SARS-CoV-2. [36] The company launched commercial production of CT-P59 in September to ensure, if trials are successful, the company can meet the urgent global demand for such a drug. Celltrion anticipates the development of CT-P59 will be complete by the first half of 2021, depending on certain clinical and regulatory milestones. [37] The company plans to go for EUA if positive results emerge from the ongoing trial.

Sixth, Vir Biotechnology and GlaxoSmithKline (GSK) have developed VIR-7831, a human anti-SARS-CoV-2 antibody that is now in phase II/III clinical trial to assess its efficacy for the early treatment of Covid-19 patients who are at high risk of hospitalisation and death. VIR7831 appears to act in two ways: preventing the virus from infecting new cells and marshalling the immune system to rid the body of infected cells. [38] About 1,300 patients across the world who have early symptomatic infection will be enrolled, with initial results expected before the end of 2020, full results by the first quarter of 2021, and potential early access within the first half of next year. [39] Phase III has begun after positive results based on an assessment of safety data. In addition, two other trials are under way – one for treating hospitalised Covid-19 patients and another for preventing symptomatic infection. [40]

Finally, a dark horse that has generated buzz among some scientists is the Prometheus initiative, which is a collaboration between Adimab, an antibody company based in New Hampshire, AcademicLabs, and the United States Army Medical Research Institute of Infectious Diseases. Armed with just $22 million in government support, the researchers have developed an antibody that has shown promising results in pre-clinical trials – it provided protection against the novel coronavirus, the SARS virus, and other similar viruses. Human trials will begin in the winter. If results carry over into clinical development, then Prometheus will have advantages over its peers, Lilly and Regeneron: First, the antibody looks as though it could protect for up to six months as opposed to a few weeks, and it can also be administered in one dose, which means that more people can benefit from it.

Challenges With Antibody Treatments: Manufacturing Capacity, Access and Equity for Poorer Countries

There are challenges with antibody-based treatments, despite emerging evidence that they are effective.

Scaling to meet demand will be challenging. The amount of antibodies injected depends on a person's weight and can be a large quantity. Their production requires specialised factories that have components such as culture media, sterile vials and purification resins. Manufacturing at scale is also difficult, as evidenced by the low numbers of doses that even major companies such as Lilly and Regeneron are able to provide. Regeneron currently has 50,000 treatment courses stocked but is working to produce 300,000 courses for the US over the next few months as part of its $450 million contract; 300,000 to 400,000 dose per month are needed just for the US. [41] Regeneron is working to meet demand by providing unfinished, bulk lots of the cocktail along with finished doses for the rest of the year; the contract with the US government also carries an option to provide between 420,000 and 1.3 million preventive doses. [42] Regeneron has signed a deal with Roche, a Swiss drugmaker, to expand production three-and-a-half fold, with the possibility of additional expansion; both companies will reserve manufacturing capacity in anticipation of regulatory approvals. [43] While Regeneron is responsible for securing FDA approval in the US, Roche assumes responsibility for non-US regulatory approvals, following the initial approval by the European Medicines Agency (EMA); additional approval-related studies required by regulators outside the US also fall under Roche's purview. [44] The deal is expected to generate $6 billion in sales per year for the company. [45] Regeneron will use its production capacity (reserving 40,000 litres of bioreactor capacity) to service the US market while Roche (100,000 litres) will be responsible for other countries; the joint effort will result in 650,000 to 2 million treatment doses, or 4 million to 8 million preventive doses, on a yearly basis. [46] The final number of doses will depend on the results from clinical trials. If lower dosages prove effective, then more cocktail will be available.

In September, Lilly and Amgen announced a deal to collaborate on global manufacturing of Lilly's Covid-19 antibody therapies, should they reach regulatory approval. Details are not currently available. The company has a deal with contract development manufacturing organisation (CDMO) Fujifilm Diosynth Biotechnologies to support manufacturing, with the Japanese company reserving its facility in Denmark, which will receive $928 million to double its capacity. [47] Set to begin commercial manufacturing in April 2021, the facility holds six 20,000-litre bioreactors that will produce the medicine, some of which will go to low- and middle-income countries; the agreement has support from the Bill & Melinda Gates Foundation, which has prioritised Covid-19 vaccines and therapeutics access for

poorer countries. [48] Takeda has also started manufacturing, producing clinical batches at a CSL site in Switzerland and Takeda's US site. It is unclear how many doses Takeda will produce by the end of 2020 because it will depend on donations of CP and the final dosage.

The challenges in producing and scaling up production have incentivised competitors to become collaborators. The Takeda-led alliance has been mentioned as an example. In June GlaxoSmithKline, AstraZeneca, Lilly, Amgen, AbCellera and Roche's Genentech collaborated to share confidential information on monoclonal antibody manufacturing in order to accelerate manufacturing process best practices in an agreement that received approval from the antitrust division of the US Department of Justice. [49] Pricing is excluded from the collaboration.

The manufacturing process is complex but is worth laying out in some detail. Duke University's Margolis Center for Health Policy explains it in the following way:

"Manufacturing of mAbs [monoclonal antibodies] generally consists of upstream processes for production of the crude protein drug via cell culture in a bioreactor followed by downstream processes for purification of the bulk drug substance and formulation and sterile filling of the final drug product. The sterile-filling process is generally a procedure that is common among sterile injectable products. As such, it can be quite amenable to contract out to multi-product filling facilities.

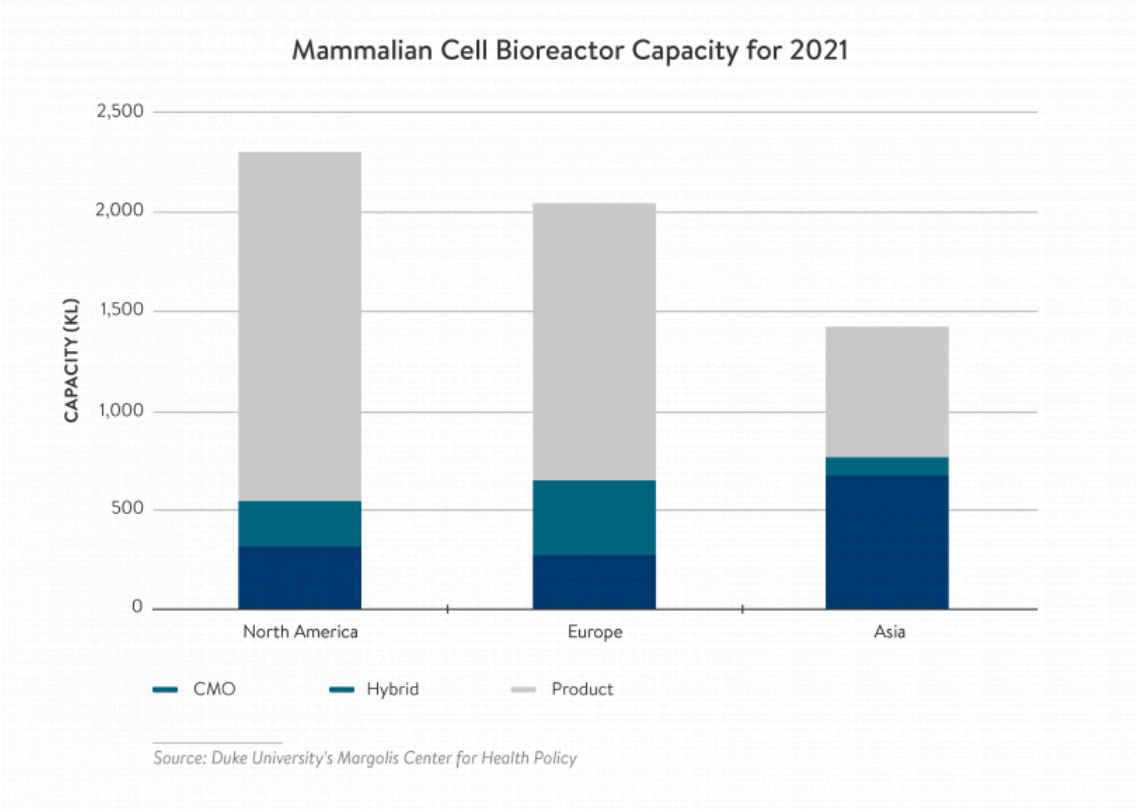
"In contrast, the fungibility of the mAb manufacturing capacity depends on the process mode and bioreactor type. Two popular bioreactor process modes are fed-batch and perfusion. Fed-batch is when the nutrient feed is added to the bioreactor during the culture process. Perfusion mode is also known as continuous and is where the nutrient feed is constantly replaced with a fresh supply. Another aspect of fungibility is bioreactor type. Stainless steel bioreactors have historically been used for large-scale production, though single-use bioreactors have become more available in recent years due to the relatively short turnaround between batches (clean-up operations are quicker) and reduced upfront investment." [50]

The UK has limited domestic large-scale manufacturing capacity as a result of the lack of financial and non-financial incentives to encourage companies to set up manufacturing sites domestically as well as a historically fragmented approach to this increasingly important area. [51] FujiFilm Diosynth Biotechnologies and Lonza Biologics –which were both members of the BIA Antibody Taskforce during its early phase but are not currently – have small-scale manufacturing capability (1,000 to 2,000 litres), which is insufficient to produce what is needed. The closest capacity is in the Republic of Ireland, but accessing it requires significant advance notice to reserve the facilities. Over time, however, the UK government has developed a more integrated strategy to increase future biologics manufacturing capacity through new modes of facilities production that will position the country for greater pandemic preparedness. This is a matter of national security, given that production is happening on a regional basis.

The UK's exit from the European Union lends greater urgency to domestic capacity expansion and creates higher hurdles from a regulatory perspective.

Figure 2 shows where bioreactor capacity is for 2021. [52] There are 200 facilities globally, with capacity distributed across contract manufacturers (CMOs), companies that use an in-house manufacturing network (product) and those that use a hybrid model of the two. [53] With the exception of one clinical Canadian facility, North America's manufacturing capacity is based solely in the US, and represents about 40 per cent of the total bioreactor volume in markets analysed by healthcare market research firm, BioTrak; 78 per cent of the capacity is with companies that manufacture in-house. [54] By Q2 of next year, 12 per cent (677 kilolitres) of the capacity shown in Figure 2 will be available with 452 kilolitres of it residing in Europe (Ireland and Switzerland) and used by product manufacturers; the US will see an increase in manufacturing capacity of just 6 per cent by January 2021, with roughly 50 per cent controlled by CMOs. [55] New capacity will become available between 2022 and 2024, 50 per cent of which will be in Europe. In Asia, Samsung Biologics stands out for its significant investments to increase manufacturing capacity. For example, AstraZeneca has signed a deal with the South Korean CMO for $331 million to produce bulk drug substance and drug product in support of AstraZeneca's biologics therapeutics at its Plant 3 Incheon facility. The deal is part of Samsung's larger plans, which include construction of a $2 billion biologics "super plant" that would become one of the largest in the world, with 256 million square feet of floor space to support 256,000 litres of capacity, which would double Samsung Biologics' total capacity to 620,000 litres. [56] The facility is set to open in 2022 and will have a footprint that is as large as its three other facilities combined. [57] Samsung is currently working on a deal to open another campus in Incheon that would include biotech companies, research and development, and more manufacturing facilities. Samsung has secured $362 million from Vir Biotechnology to scale the latter's monoclonal antibody programme for Covid-19; Samsung is in the process of manufacturing the product with the goal of producing commercial amounts, beginning in 2021. [58]

Figure 2 – The geographic spread of bioreactor manufacturing capacity



A possible way around the challenge is to explore the advances made in construction of such plants. Traditional fixed-manufacturing facilities can take more than six years to construct, while more modern modular platforms can be built in a matter of 18 months. The drawback, however, is that such platforms have lower capacity. While there are questions around their availability and the process for rendering them operational, another possibility could be to refurbish facilities that are no longer being used.

The manufacturing challenges outlined above raise important policy issues regarding how to maximise the quantity of treatment made given constraints on manufacturing capacity. One proposal is for production to be moved flexibly and quickly between various facilities to make the most of whatever production capacity is available, without generating shortages of critical non-Covid-19 biologics. This is not, however, optimal. For a biologic like an antibody, the process *is* the product. Changing from one site to another is not trivial and carries the risk that the product will be altered. This is another good reason to prioritise consistent local sourcing in any strategy. Currently, manufacturers act on an individual basis in terms of securing manufacturing facilities. One challenge with this arrangement is that manufacturers that reserve production capacity in advance may generate difficulties in matching scarce available supply with the specific monoclonal antibodies that show efficacy. [59] The second challenge is that manufacturers assume financial risk to ensure supply should their medicine reach approval, which means they may not have enough resources to make big enough investments to meet demand. [60] The rising new wave of Covid-19 infections this autumn means the need for these products is all the more urgent.

Industry coordination could begin to deal with these challenges, and the work of the UK Bioindustry Association is engaged in these issues. Such collective action problems lend themselves to government intervention in the form of coordination and financial support, which is part of what the US government did with relaxing laws on anti-trust activity to enable industry coordination, as well as with Operation Warp Speed, which invested in expanding manufacturing capacity for credible vaccine candidates. Government can help with financing expansion of manufacturing capacity (both by supporting expanded capacity for production and storage of non-Covid-19 drugs so that additional space is available for monoclonal antibodies), contractual arrangements among manufacturers, and technology transfer. [61] A dedicated forum for government regulators and manufacturers would ensure that these moves happened in an orderly way. It would also allow them to work together to quickly yet rigorously review and fast-track approval so that these life-saving drugs could be made available as quickly as possible.

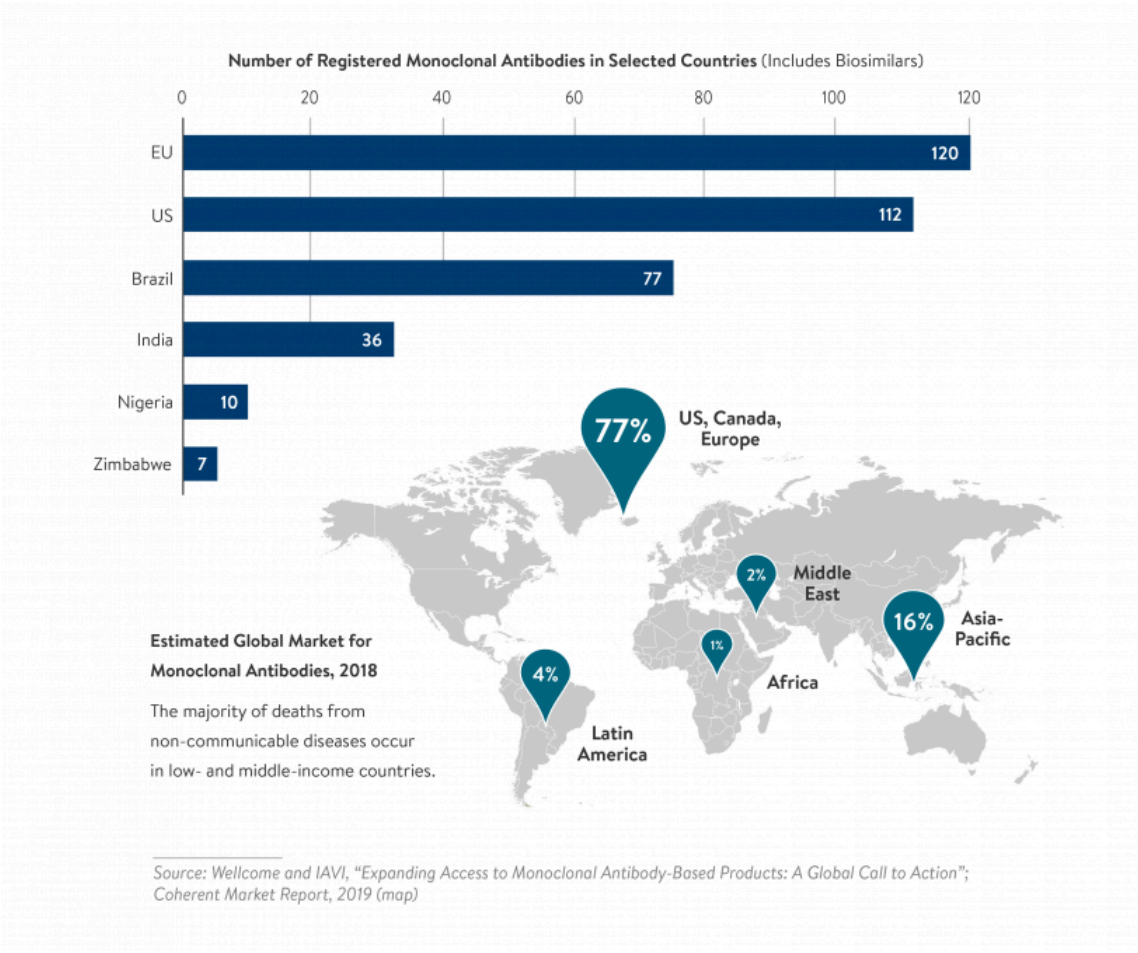
A second challenge relates to cost. Antibodies are expensive, and can range between $15,000 and $200,000 for a year's worth of treatment; the price depends on dose level, frequency and other variables, and is likely to be prohibitive for most of the world's countries. [62] If monoclonal antibodies are expensive in rich countries then they are most certainly all but out of reach for low- to middle-income countries that are also struggling with the pandemic (see Figure 3). The global market is skewed towards the US, Canada and Europe, which hold 80 per cent of the market for monoclonal antibodies, with the remainder lying in the rest of the world. [63] In the absence of concerted action, this imbalance will continue. In its recent report, "Expanding Access to Monoclonal Antibody-Based Products", Wellcome and the IAVI stated: "Few, if any, monoclonal antibodies are registered in low-income countries, and those that are registered in many middle-income countries are often unavailable in their public health systems, making them prohibitively expensive. This gap in access will only widen because monoclonal antibodies are an increasingly large proportion of pharmaceutical company pipelines." [64] Middle-income India is a partial exception, due to its robust drug-making ecosystem, including biosimilar manufacturing capacity. [65]

The two factors that impact access are availability and affordability; each is considered in turn. With respect to the former, many monoclonal antibody-based treatments are not available in poorer countries, often due to drug companies' preference for commercialisation in richer markets while inefficient regulatory processes around filing, approval and launch of these treatments in poorer countries, resulting from capacity constraints, also hinder availability. [66] Wellcome's analysis suggests ways to ameliorate the problem:

- Harmonise and expand existing policy and regulatory pathways and explore new ways to encourage wider registration of mAbs (monoclonal antibodies) in low- and medium-income countries.
- Raise awareness of the clinical, public health and economic value of mAbs through concerted advocacy efforts.

- Strengthen health-care systems and the ability to diagnose disease in LMICs to support a more accurate assessment of the market need for mAb products and to enable their implementation. [67]

Figure 3 – An overview of the global monoclonal antibodies market



Even with the rise of biosimilar products manufactured in India, monoclonal antibody-based treatments remain out of reach for most of the world. According to the Wellcome analysis, possible routes to lowering their price include:

- Investing in and deploying innovative technologies to lower monoclonal antibody development costs.
- Establishing collaborations between public, private and philanthropic entities to expand access to innovative and biosimilar mAbs in low- and middle-income countries. [68]

The nature of the pandemic is such that political leaders, policymakers, and a good swathe of the general population in developing countries are broadly aware that a range of treatments is under clinical development, which is important for generating advocacy around ensuring greater access. The Access to Covid-19 Tools (ACT) Accelerator has a pillar devoted to therapeutics that features a strategy for

addressing the range of challenges in addressing access and equity for poorer countries. There are three workstreams that, if fully funded, will require $7.2 billion over 12 months:

1. Rapid evidence assessment of candidates, coordinating the clinical trials portfolio, scientific direction and selection of candidates for development at scale (including evaluation beyond the current portfolio of Therapeutics Accelerator candidates).
2. Market preparedness, facilitating market entry and supply at scale, including regulation, production capacity, pricing, designing appropriate tools and interventions adapted to the specific product.
3. Adequate deployment in all countries, ensuring procurement, equitable distribution and delivery at scale and in all settings. [69]

It is difficult to see how access to antibody-based treatments in poor countries will secure the same level of political and support and public attention as vaccines, despite the deal signed by Lilly to produce its treatment for poorer countries. The reality is that until weaknesses in the poor countries' hospital systems can be addressed, antibodies may only be feasible at scale in more developed health-care systems. The encouraging news is that a number of African countries have managed the pandemic through mass testing, tracing, shielding the vulnerable and wearing face masks. Other drugs such as dexamethasone are more feasible for poorer countries: the drug is affordable, available, and is on the WHO's list of essential medicines.

Bridging the Gap: Secure Access Now While Planning for the Future

Antibody treatments – assuming they are approved – must be as central to pandemic management as vaccines. Antibody and vaccine deployment strategies need to be closely aligned and able to respond to the data as they come out. For example, if vaccine efficacy proves to be lower than expectations, then the importance of antibodies to the pandemic management strategy will increase. If and when antibody-based treatments are authorised, they should be used for the most vulnerable populations such as those in care-home settings, the elderly (whose immune systems are less responsive to vaccines), frontline health workers, and people with underlying conditions that are not suitable for vaccination. The last category may require prioritisation given the challenge of scaling up production of these treatments, which is expensive. The key point is that fewer doses of antibodies will be required as compared to vaccines. This is good news given the challenges of securing access and scaling up production quickly.

Bringing antibody-based treatments to market in a timely fashion is critical. In the US, non-Covid-19 monoclonal antibody drugs are quite common already and tend to move through regulatory approval processes quickly under normal circumstances; according to some experts it should be possible to skip some of the steps as a result of the pandemic and issue full approval for them. [70] In the UK, innovations in the clinical development process have led to a partnership between regulators, scientists and drug companies in ways that allow for greater efficiency in the process, such as real-time data analysis and adjustments so these treatments can reach regulatory approval more quickly, without compromising efficacy and safety.

Currently there is a global shortage of antibody doses for Covid-19, including in the UK, which lacks large-scale manufacturing capability. Technological innovation has led to new ways of scaling up biologic manufacturing facilities, specifically modular designs for small-scale capacity (up to 2,000 litres). In this approach, many processes are disposable and the relevant components (such as plastic bags and rubber tubing) may be at risk of being in short supply. Attention to the supply chain will be important as demand for Covid-19 antibody treatments surges.

Small-capacity, modular production facilities likely will produce a few thousand doses but will take several months to get up and running. The UK government has developed a more integrated strategy to increase future biologics manufacturing capacity that will position the country for greater pandemic preparedness. This is a matter of national security, given that production is increasingly regional. The UK's exit from the European Union lends greater urgency to domestic capacity expansion and creates higher hurdles from a regulatory perspective.

Coordinated action, with governments playing a central role, will be critical to addressing the constraints on mass production of antibodies. Financial support to the industry, enabling short-term construction of modular facilities, and facilitating collaboration between companies to allow for sharing best practices in order to speed up manufacturing are all important policy priorities. The material point is that government leaders need to be nimble and flexible in order to bring critical drugs to market safely yet quickly.

Governments are currently being forced to develop strategies to cope with the hard realities of spikes in new infections, public fatigue with restrictive measures, and weakening economies. The focus throughout the pandemic – at least in the public imagination – has been the development of a vaccine; this is also where most public funding has gone. The popular understanding of vaccines is that at their best, they eradicate disease and prevent people from becoming sick. The reality is that the first generation of Covid-19 vaccines may resemble the influenza vaccine with respect to efficacy, which hovers at 50-60 per cent.

Antibodies are therefore very likely to be an important element in a toolkit to manage Covid-19 along with robust mass testing, tracing and quarantining; shielding of the vulnerable; good hand hygiene; social distancing; and the widespread use of masks (which will continue to be needed). Challenges notwithstanding, antibodies will be a powerful bridge to any vaccine that is eventually approved.

Table 1: Drugs under clinical development to treat Covid-19

Drug [71]	**Developer/ Researcher**	**Sponsor**	**Phase**	**Type/Target family**
Pepcid (famotidine)	Yamanouchi Pharmaceuticals; J&J; Merck	Northwell Health	Phase III	**H2 blocker**
Bucillamine	Revive Therapeutics, LTD		Phase III	Anti-rheumatic agent

Drug [71]	Developer/ Researcher	Sponsor	Phase	Type/Target family
Lenzilumab	Humanigen; Catalent	NIAID	Phase III	Monoclonal antibody
Ilaris (canakinumab)	Novartis	Novartis	Phase III	Monoclonal antibody
Farxiga (dapagliflozin)	Bristol-Myers Squibb Astra Zeneca	AstraZeneca	Phase III	Oral sodium-glucose co-transporter 2 (SGLT2) inhibitor
Ultomiris (ravulizumab)	Alexion	Alexion	Phase III	Monoclonal antibody
Losmapimod	Fulcrum Therapeutics	Fulcrum Therapeutics	Phase III	Mitogen-activated protein kinase (MAPK) inhibitor
Kaletra (lopinavir/ ritonavir)	AbbVie	UK government, (University of Oxford RECOVERY Trial) LifeArc (FLARE trial)	Phase II/IV	HIV protease inhibitor

Drug [71]	Developer/ Researcher	Sponsor	Phase	Type/Target family
Metformin (Glucophage, Glumetza, RIomet)	University of Minnesota	University of Minnesota	Phase II/III	Biguanide
Niclocide (niclosamide)	ANA Therapeutics	Tufts Medical Center; First Wave Bio, Inc; Lille University Hospital	Phase II/III	Anthelmintic
Velklury (remdesivir)	Gilead Sciences	Gilead Sciences	Phase II/III	Antiviral
PTC299	PTC	PTC	Phase II/III	Dihydroorotate Dehydrogenase (DHODH) inhibitor
RLF-100 (aviptadil)	NeuroRx; Relief Therapeutics	NeuroRx	Phase II/III	Synthetic human vasoactive intestinal peptide (VIP)
Actemra (tocilizumab)	Roche		Phase III	IL-6 receptor agonist

Drug [71]	Developer/ Researcher	Sponsor	Phase	Type/Target family
ABX464	Abivax	Bpifrance	Phase IIb/III	HIV-1 Rev protein inhibitor
Rhu-pGSN (gelsolin)	BioAegis Therapeutics	Unknown	Phase II	Recombinant human plasma
EIDD-2801, oral ribonucleoside analog	DRIVE; Ridgeback Biotherapeutics; Merck	Unknown	Phase II	Antiviral
LAM-002A (apilimod dimesylate)	AI Therapeutics, Inc;	AI Therapeutics, Inc.; Yale University	Phase II	PIKfyve Inhibitor
Convalescent plasma	Multiple	Multiple	Phase I/ Phase II	Immunoglobulin
AdMSCs	Celltex Therapeutics	Celltex Therapeutics	Phase II	Autologous adipose-derived stem cells

Drug [71]	Developer/ Researcher	Sponsor	Phase	Type/Target family
Remicade (infliximab)	Janssen	UHB; Birmingham National Institute for Health Research Biomedical Research Centre; NIHR BRC)	Phase II	Monoclonal antibody
Calquence (acalabrutinib)	AstraZeneca	AstraZeneca	Phase II	Kinase inhibitor
Gimsilumab	Rolvant Sciences	Rolvant Sciences	Phase II	Monoclonal antibody
Otilimab	MorphoSys; GSK	GSK	Phase II	Monoclonal antibody
STI-5656 (abivertinib)	Sorrento Therapeutics		Phase II	Tyrosine kinase inhibitor
Humira (adalimumab)	University of Oxford	Covid-19 Therapeutics Accelerator	Phase II	Anti-TNF

Drug [71]	Developer/ Researcher	Sponsor	Phase	Type/Target family
COVI-GUARD (STI-1499)	Sorrento Therapeutics	Sorrento Therapeutics	Phase I	Monoclonal antibody
JS016	Lilly; Junshi Biosciences	Lilly	Phase I	Monoclonal antibody
DNL 758 (SAR443122)	Sanofi/Denali Therapeutics	Sanofi	Phase Ib	RIPK1 inhibitor
REGN-COV2	Regeneron	Regeneron	Phase I/II/III	Antibody cocktail
PTC299	PTC	PTC	Phase II/III	Dihydroorotate dehydrogenase (DHODH) inhibitor
LY-CoV555	Lilly;AbCellera	Lilly; Operation Warp Speed	Phase I/II/III	Monoclonal antibody

Table 2: Clinical studies evaluating anti-SARS-CoV-2 monoclonal antibodies

Sponsor	Drug Code	Status	Est. Start Date	Est. Primary Completion
Junshi Biosciences / Eli Lilly and Company	JS016	Phase I	6/5/2020	December 2020
Tychan Pte. Ltd	TY027	Phase 1	6/9/2020	Oct 2020
Brii Bioresources	BRII-196	Phase I	7/12/ 2020	Mar 2021
Brii Biosciences	BRII-198	Phase I	7/13/ 2020	Mar 2021
Sinocelltech Ltd	SCTA01	Phase I	7/24/ 2020	November 2020
Sorrento Therapeutics, Inc	COVI-GUARD (STI-1499)	Phase I	9/17/ 2020	February 2021
Mabwell (Shanghai) Bioscience Co., Ltd.	MW33	Phase I	8/72020	December 2020

Sponsor	Drug Code	Status	Est. Start Date	Est. Primary Completion
Sorrento	COVI-AMG (STI-2020)	Phase I/ Phase II pending	December 2020	April 2020
Hengenix Biotech Inc	HLX	Phase I pending	12/0/ 2020	September 2021
Beigene	BGB DXP593	Phase I Phase II	8/31/ 2020 10/30/ 2020	10/15/ 2020 2/28/2021
AstraZeneca	AZD7442 (AZD8895 + AZD1061)	Phase I Phase III pending	8/17/ 2020	September 2021
Celltrion	CT-P59	Phase I Phase III	7/18/ 2020 10/1/ 2020	November 2020 NA

Sponsor	Drug Code	Status	Est. Start Date	Est. Primary Completion
Vir Biotechnol./ GlaxoSmithKline	VIR-7831/ GSK4182136	Phase II/ Phase III	8/24/ 2020	January 2021
AbCellera / Eli Lilly and Company	LY-CoV555 (LY3819253) combination of LY-CoV555 with LY-CoV016 (LY3832479)	Phase III (paused)	5/28/ 2020; 6/ 13/2020; 8/1/2020; 8/4/ 2020; Aug 2020	8/23/ 2020; 9/ 15/2020; 3/8/2021; July 2021; Sep 2020
Regeneron	REGN-COV2 REGN10933 + REGN10987	Phase I/II Phase I/II Phase III	6/9/2020 6/12/ 2020 6/30/ 2020	11/21/2020 3/13/2021 4/11/2021

Source: "Covid Biologics Tracker", Antibodies Society

Footnotes

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