Global Insight: Market update

RBC Wealth Management

COVID-19: The earnest search for the ultimate salve

COVID-19 has brought companies and countries together for a common goal. We examine that search for treatments and vaccines.

At the time of writing, the global COVID-19 case count has surpassed the 2 million mark. The unprecedented nature of this crisis, the toll on human life, and the uncharted territory from an economic and markets standpoint can feel ominous. The world's lack of preparedness for a global pandemic, from medical and economic perspectives, is without question. Yet, despite what seems to be insurmountable uncertainty, our view is that this too shall pass.

The question is more when, not if. The answer to the former relies heavily on the success of physical distancing globally to contain the spread and give the global health care system a fair shake at treating those with severe illness. But importantly, it also relies on the development of drug treatments and vaccines, and we would argue on this front, there are silver linings. That is to say, the singular focus of health care organizations, research labs, and scientists worldwide is to find a cure and vaccine for COVID-19. The rate at which resources have been rapidly mobilized in advancement of treatment, and the level of coordination and collaboration amongst health care professionals and information sharing across borders is unprecedented. As of the time of writing, there are 614 clinical trials for drug treatments for COVID-19, and 78 vaccine programs underway.

This article seeks to highlight potential new drug therapies and vaccines under investigation. Note that this discussion is not intended as a recommendation of ownership of the companies involved in these trials. Rather, we look to underscore important medical developments related to COVID-19 that we believe provide grounds for some optimism against the constant barrage of negative

headlines. In the appendices, we provide a few examples of global coordination across the health care industry.

Therapeutics versus vaccines – The race versus the marathon

It's important to distinguish between therapeutics and vaccines. Therapeutics, or more simply medications, are given to people who are sick, and therapeutic trials are given to those who are very sick, reactively. The hope with the drug is that it delays the infection, treats the infection, and hopefully makes people better.

Vaccines are given to a healthy population proactively to boost the individual immune system to produce antibodies and protect the individual from future exposure to the virus. So, while a COVID-19 drug treatment could conceivably be administered to thousands of very sick patients, a vaccine would be given to hundreds of millions

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(if not billions) of healthy people globally. A vaccine must be safe and effective for it to be rolled out on a mass basis worldwide—there are no shortcuts.

Vaccines are amongst the greatest achievements in public health care, though not without a history of controversies. In the late 60s, babies and toddlers that were immunized against Respiratory Syncytial Virus (RSV) experienced serious side effects including high fever, wheezing, and pneumonia when exposed to the natural wild type of virus.

There are always risks in designing a new vaccine. The faster and greater the shortcuts, the more risky the vaccine will be. A best-case scenario may be that a vaccine is developed within a year according to industry experts and medical articles.

It's not just about rushing the science but also the manufacturing—global supply chains must be equipped to manufacture the vaccine in huge amounts. Furthermore, when developed, vaccines will only be effective with buy-in from the public. Put differently, vaccines are effective in controlling breakouts if enough people get vaccinated to build so-called "herd immunity". Even if vaccines are mandatory, compliance with such a measure, particularly during a public health emergency, is not a foregone conclusion especially since there are still sizeable portions of society that believe, vehemently, that vaccines are not just unnecessary, but harmful. That said, in light of how COVID-19 has brought the world to a standstill, perhaps such views may be altered.

Some vaccines under investigation:

Notwithstanding the complexities and extended timeline for a vaccine to be developed, there are more than 75 vaccines in early-stage development. Below is a sampling.

- **Moderna (MRNA):** This vaccine program has perhaps received the most attention. MRNA, a biotech company that develops vaccines and therapeutics, has already begun dosing patients with its experimental COVID-19 vaccine. Very recently, Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases, stated that the vaccine was "on track". The clinical trials require the vaccine to be administered in three doses to human volunteers. The first two doses have been tested, and a large third dose is being administered to check for adverse reactions. Though the vaccine is being fast-tracked, it would still be another 12–18 months before it can be made available at a mass scale even if it's approved for use, according to the company.
- **Johnson & Johnson (JNJ):** The world's largest pharma company was one of the first to announce a COVID-19 vaccine program. JNJ has said that the vaccine could be available for emergency use early next year, and manufacturing is underway. The plan is to begin human testing by September. JNJ plans to make the vaccine available "on a not-for-profit basis for emergency pandemic use". It has been working on a vaccine since January partnering with the Biomedical Advanced Research and Development Authority (BARDA), a division of the Department of Health and Human Services. The partnership has pledged $1 billion towards the development of a vaccine.
- **Pfizer (PFE) and BioNTech (BNTX):** BNTX is a German biotech company that specializes in vaccines. In mid-March, PFE announced the signing of a letter of intent with BNTX for the co-development and distribution of a coronavirus vaccine aimed at preventing COVID-19 infection. The recent partnership builds on a 2018 agreement to jointly develop an influenza vaccine. The additional agreement covers co-development and co-commercialization (ex-China) aimed at accelerating the development of BNTX's COVID-19 vaccine. Trials begin at the end of this month in the U.S. and Europe. The partners have also announced there are plans to scale up manufacturing capacity to produce millions of doses of vaccine during 2020 and escalate that into hundreds of millions during 2021.
- **Sanofi (SNY):** SNY is collaborating with Translate Bio (TBIO) on a COVID-19 vaccine, with the hopes to begin testing by the end of this year and approval by the second half of next year. Separately, in February, SNY announced a collaboration with BARDA to advance another type of vaccine for the disease.
- **Tuberculosis vaccine and COVID-19:** A preliminary study posted on medRxiv, a website for unpublished medical research, has found a correlation between countries that require citizens to get the Bacillus Calmette-Guérin (BCG or tuberculosis) vaccine and those showing fewer confirmed cases and deaths from COVID-19. While correlation is not causation, clinicians in at least six countries are running trials that involve giving frontline health workers and elderly people the BCG vaccine to see if it provides some level of protection against the novel coronavirus. The study was initiated when it was noticed that countries including Japan and South Korea, which have universal BCG vaccine policies, have better controlled the disease in the absence of a nationwide lockdown. Key players in

the BCG vaccine segment include Merck (MRK) and SNY.

All told, even if we examine an exhaustive list of vaccines under consideration, the timeline until one becomes available on a scaled basis, is likely at least a year out. A year seems like an inordinate amount of time in the context of nationwide lockdowns and strict guidelines around physical distancing. Yet there is still hope therapeutics, which could become available sooner than a vaccine, at a minimum can alleviate the symptoms of those with the most severe cases of the illness and, at best, ultimately provide a cure.

Some drug treatments under investigation:

Below we highlight a number of drug treatments for COVID-19 under consideration, though by no means is it an exhaustive list.

- **Remdesivir by Gilead (GILD):** This drug was initially developed for the treatment of Ebola during the 2014–2016 outbreak. While other drugs were ultimately used, the WHO has described Remdesivir as the best hope to treat the disease until a vaccine becomes available. Though China recently halted its planned trial due to poor enrolment as a result of the virus waning in the region, trials continue in the U.S. Gilead expects early data from its trial of the drug in severe patients at the end of this month, and data from a trial testing it in patients with moderate symptoms by May. Furthermore, BBC reports indicate the UK government has fast-tracked the trials, and there will be two studies carried out in the UK—one in patients with moderate symptoms and one on those who are in serious condition. In studies of mice and human cell cultures, this anti-viral showed some promise in inhibiting the viruses that cause SARS and MERS, which are both coronaviruses as is COVID-19.
- **Hydroxychloroquine and chloroquine (produced by Mylan [MYL], Teva [TEVA], Novartis [NVO], and Sanofi):** The Food and Drug Administration (FDA), on March 29, issued an emergency use authorization for hydroxychloroquine and chloroquine—decades-old malaria drugs—for the treatment of COVID-19. The agency allowed the drugs to be "donated to the Strategic National Stockpile to be distributed and prescribed by doctors to hospitalized teen and adult patients with COVID-19, as appropriate, when a clinical trial is not available or feasible". The FDA has already allowed New York state to test administering the medication to seriously ill patients, and some hospitals have added it to their treatment protocols. Still, scientists have noted the lack of data on the drugs' efficacy for coronavirus care and are concerned it would crowd out patients who need the drugs for other serious conditions. Early data from a study conducted at the University of Wuhan showed the use of hydroxychloroquine resulted in cough, fever, and pneumonia receding faster, while the disease seemed less likely to turn severe for patients that received the drug, versus a comparison group that was not given the drug. The authors of the report said the medication was promising, but that more research was needed to clarify how it might work in treating coronavirus disease and to determine the best way to use it. In contrast, however, in a recent French study, doctors looked back at medical records for 181 patients with COVID-19 who had pneumonia and required supplemental oxygen. Roughly half had taken hydroxychloroquine within 48 hours of being admitted to the hospital, the other half had not. The doctors followed the patients and found there was no statistically significant difference in the death rates of the two groups, or their chances of being admitted to the intensive care unit. The study also raised important safety concerns around the drug. For example, in the study, eight patients who took the drug developed abnormal heart rhythms and had to stop taking it. Similarly, doctors in Sweden and Brazil have warned of similar side effects with the use of chloroquine.
- **Kaletra by AbbVie (ABBV):** This is essentially a combo therapy, made up of two drugs, lopinavir and ritonavir. It is produced by AbbVie for the treatment of human immunodeficiency virus (HIV). In mid-March, it was reported that the drug failed across the board in a 199-patient clinical trial. Furthermore, it did not improve clinical symptoms nor extend lifespan in patients hospitalized with severe COVID-19. That said, there may be potential for this drug in patients for whom the drug is initiated soon after they show symptoms, but before the symptoms become severe. In patients that received Kaletra earlier, a clearer mortality benefit was demonstrated. According to an article in the Financial Times, in a drastic step to open Kaletra to competition, ABBV will not enforce global patent rights on all formulations of the HIV medication as the drug is being evaluated to treat severe COVID-19 in several clinical trials. The move comes after shortages in several drugs that are being tested for the treatment of COVID-19.
- **Actemra:** The drug, produced by **Roche (RHHBY)**, has already been approved in China for the treatment of patients infected with COVID-19 that have developed serious lung damage. The drug, used primarily for

the treatment of rheumatoid arthritis, has recently been approved by the FDA for a Phase 3 trial (named COVACTA) in severely ill COVID-19 patients, who have been hospitalized with pneumonia. Roche has also committed to providing 10,000 vials of Actemra to the U.S.'s Strategic National Stockpile for potential future use.

- **Sarilumab:** This drug is also known under its brand name Kevzara, and was approved by the FDA in 2017 for the treatment of rheumatoid arthritis. The drug was developed collaboratively by **Sanofi** and **Regeneron (REGN)**. It is an antibody that may help suppress the immune response that causes so much damage in patients with COVID-19. The companies initiated a Phase 2/3 trial in Italy, Spain, Germany, France, Japan, Canada, and Russia. SNY and REGN are testing the drug in patients hospitalized with severe disease. SNY is leading the trials outside the U.S., with REGN handling trials within the U.S. The European trials are expected to enroll approximately 300 patients, according to company information.
- **Avigan:** Also referred to by its generic name, favirpiravir, Avigan is produced in Japan by a subsidiary of Fujifilm. The company has begun Phase 3 clinical trials to test the effectiveness of the anti-flu drug in treating patients with COVID-19, following promising results in China. Trials in China suggest Avigan could play a role in shortening the recovery time for patients infected with novel coronavirus. The trial will be conducted on 100 patients until the end of June, according to the company. Fujifilm is expanding manufacturing capacity at its Toyoma facility to speed production of Avigan, and has established strategic partnerships with domestic and overseas companies to source raw materials for the drug. With the ramp-up in production, Fujifilm is aiming to make 100,000 treatment courses of Avigan available by July—3.5 times the supply in March—and a total of 300,000 courses ready by September. The Japanese government will set aside 2 million treatment courses for its national stockpile, according to the company, which is also in discussions with foreign governments to provide additional supply.

Clinical trials are a considerable undertaking. Patience is required given the time needed for patient enrollment, running the trials, and interpretation of results. Critically, the trials that matter the most are the ones with a sizeable patient population that can yield statistically significant results. It's worth noting that effective treatments were found for Ebola after clinical trials were carried out between 2014 and 2015 in poor countries, ravaged by conflict and with little health infrastructure. While Ebola did not evolve into a pandemic, the world's health and technological capabilities and infrastructure are far more advanced today than they were five to six years ago.

Granted, in the face of daily tragedy and barrage of negative headlines, it is difficult to stay focused on the after rather than the now. However, we remain encouraged by the pace at which health care entities around the world are working to find a cure and/or vaccine, and what seems to be hyper-collaboration and coordination not seen before. As such, we choose to be cautiously optimistic—at a safe distance of course.

Appendix I: SOLIDARITY trial

The multinational trial, aptly named SOLIDARITY, will test four potential treatments for COVID-19. The trial is being coordinated by the WHO with the goal to enroll thousands of patients worldwide. Participating countries are Argentina, Bahrain, Brazil, Canada, France, Germany, Indonesia, Iran, Norway, Peru, Qatar, South Africa, Spain, Switzerland, and Thailand.

Given that a vaccine is still at least a year or more away, the aim of SOLIDARITY is to identify treatments for COVID-19 as quickly as possible to mitigate the toll of the disease. Should the trial be a success, doctors around the world will finally have evidence-based research for deciding which drugs to use, and perhaps more importantly not use, when treating COVID-19 patients with severe symptoms.

Following the 2014 outbreak of Ebola in West Africa, the WHO was criticized for its slow response. As a result, it created the R&D Blueprint as a means to ensure that the world would be better prepared for future outbreaks. The purpose of the Blueprint is to fast-track drugs and vaccines for serious and sudden outbreaks, like COVID-19.

While there are 614 clinical trials, many are small and are testing a random number of different agents (antibodies or vaccines). Some trials have had unintended negative consequences. For example, after doctors in France published a tiny study (24 patients) about the potential effectiveness of hydroxychloroquine in conjunction with azithromycin (an antibiotic) for COVID-19 patients with severe symptoms, the report was referenced in a White House tweet that called the drug a "game changer". However, many scientists have been critical of deficiencies in the study's methodology. Subsequently, there were widespread reports of panic buying, drug shortages, and even deaths resulting from attempts by some people to self-medicate with chloroquine—a drug similar to hydroxychloroquine, though more toxic. Incorrect doses can cause coma, seizures, and death. The shortages impact not only patients with COVID-19 for whom the drug may be considered, but patients with other conditions for which chloroquine is primarily used (e.g., lupus and rheumatoid arthritis).

Trials such as SOLIDARITY are critical in that they are much larger population studies from which conclusions can be drawn with statistical significance. Data about patients will be collected and given to the WHO, where it will be consolidated with other international data, and ultimately interpreted. The study is built such that there is flexibility in introducing new drugs should they show some promise. The timing of the study will ultimately depend on how effective (or ineffective) the trial treatments are, and the number of patients ultimately enrolled.

Appendix II: COVID-19 Therapeutics Accelerator

A consortium of life sciences companies has announced plans to collaborate in the development and manufacture of vaccines, and diagnostic and treatments for COVID-19 in response to the novel coronavirus pandemic. This consortium, the COVID-19 Therapeutics Accelerator, was launched recently by the Bill and Melinda Gates Foundation, along with Wellcome (a research-charity based in London, UK), and Mastercard. It is designed to pool global resources and expertise and speed up research and development in the fight against the pandemic, and is working in tandem with the WHO, national governments, business sectors, and organizations to deliver end-to-end results "from drug pipeline development through manufacturing scale-up" with a focus on ensuring that these products are "accessible and affordable to people in low-resource settings".

The founding entities have led funding with $125 million. Most recently the Chan Zuckerberg Initiative, a philanthropic foundation established by Dr. Priscilla Chan and her husband Mark Zuckerberg, co-founder of Facebook, committed $25 million to the Therapeutics Accelerator.

Pharma companies participating include **Eli Lilly (LLY)**, **GlaxoSmithKline (GSK)**, **Johnson & Johnson**, **Merck**, **Novartis**, **Pfizer**, and **Sanofi**.

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