COVID-19 – Perspective from a Biotech Investor Part 2

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It has been just five weeks since we published our first note on the COVID-19 pandemic and summarized the unprecedented medical and scientific efforts underway to avert a humanitarian disaster.

In this note, we aim to give an update on progress made so far in the key areas of diagnostics (testing), therapeutics and treatments (both to prevent infections from becoming severe and treating those who do become dangerously ill) and vaccines (protecting people from infection).

The joint scientific effort to address the problem has been the first of its kind, yet one thing is very clear: it is society and not technology which is flattening the curve. The active participation of people, healthcare workers, patients and the general population is mitigating the crisis and the main weapon against this pandemic. Without social distancing, quarantine and wearing of protective clothing etc. – the situation would be far worse. Perhaps one of the most surprising aspects of this pandemic is our reaction to it and how quickly people around the world have adapted, in spite of the hardships imposed. This is a global battle in which everyone must participate: we win or lose this together.

What happened in the area of diagnostics?

In less than a month, the landscape has changed and indeed improved dramatically with regard to the availability of diagnostic tests for COVID-19. Today, there are over thirty testing kits available on the market. Production is ramping up, such that the availability of diagnostics tests should no longer be a bottleneck in the fight against the disease. The speed of progress and the hands-off attitude of the regulatory agencies allowing tests to come to market much quicker than ever seen, is obviously driven by the urgent need for fast (but also reliable) testing.

As outlined in our previous note, there are two main categories of tests: those that detect the virus itself (or viral particles) and those that detect *antibodies* to the virus. The first are genetic/molecular tests that are conducted by taking nasal swabs and then isolating and amplifying the genetic material of the virus to detect and diagnose an ongoing viral infection. The second are the serological tests/assays that measure antibodies specific to a particular virus in a blood sample and identify those people who have generated an immune response to the virus. The antibodies to the virus are only detectable 7-21 days *after* initial infection. For that reason these tests are less suited to diagnosis of active infection. Now that hospitals and medics are much more familiar with COVID-19 and its symptoms, a diagnosis of active infection is predominantly made based on clinical presentation – regardless of the test results.

The US and EU regulatory agencies – the FDA and EMA respectively - have eased the requirements for these antibody based tests to allow them to reach the market faster. A great step for society. This does however also mean that both sensitivity and specificity of these tests – being the two key qualitative criteria for any test - may be *lower* or not as clearly characterized than what would have been acceptable if the regulatory agencies would not have eased requirements. They may be – somewhat - less reliable. The agencies – and society – find this acceptable because these tests are not used to diagnose the active infection. In other words, doctors do not have to base a treatment decision on the outcome of these tests, meaning that they effectively carry less risk when used. In

addition, they are much less complex to perform than the molecular tests and – last but not least - there is a huge and urgent need to obtain medical data allowing our governments and their advisors to base their decisions on. It is these antibody based tests that will in fact be critical to our governments' decisions in reopening society.

This easing of standards can create problems relating to the reliability of these tests. Different tests can give different results – leaving the physician to ponder the potential clinical significance of the results. That being said, we would expect the test performance from major vendors to be solid. The presence of antibodies is usually associated with immunity or protection from re-infection. However, we do not know the level of antibodies you need for protection or how long this protection could last.

Why is testing the cornerstone to reopening society and what are its limitations?

Dr. Fauci, Director of the US National Institute of Allergy and Infectious Disease, has proposed a passport-like system based on results of serology tests to allow people to return to work. A positive serology test result implies that sufficient neutralizing antibodies are present to provide protection against re-infection. Simple really. Unfortunately not. Here is why: at this point it is not known – not to Dr Fauci nor anyone else - what level of antibodies you need for protection or how long this protection could last. Perhaps we can distill some comfort from studies in people who survived SARS and MERS (both caused by coronaviruses). These studies suggest that immunity lasts between 2 and 3 years. This would be good news if it is also true for SARS-CoV-2. We still do not know what the cut-off level is (the level of antibodies you need to detect) and we do not know how long immunity would last. Therefore many experts believe that even when the mobility restrictions are lifted, social distancing initiatives will still be necessary to prevent a resurgence in infections.

The experts generally agree that widespread testing and contact tracing will be crucial to keeping the infection under control. It is known that many people infected with SARS-CoV-2 have no symptoms, i.e. are asymptomatic. Based on studies conducted in Wuhan, experts believe the ratio of asymptomatic to symptomatic patients is 2.5 to 1. This means that approximately 40% of infected patients have a reported diagnosis. Again, based on Wuhan numbers, approximately 2% of the city's population are thought to have been infected with COVID-19. By simple extrapolation – the level of testing needed to do effective contact tracing and to re-open society is enormous. Estimates vary between 750,000 to 1,400,000 tests per week, in the US alone.

The ideal scenario is that people can have a simple blood test to tell them if they have had the infection and are now protected from reinfection. But are the currently available tests fit for purpose? It is thought that current serology tests have sensitivity (detect even low levels of antibodies) and specificity (detect antibodies specific to the virus) in the range of 90%. This sounds pretty good until you flip that number around and realize that if 100 patients are tested – 10 will have a false result. This gets more complicated when you understand the role "prevalence" plays in this calculation. If we take the Wuhan prevalence number of 2%: if 100 people are tested you could expect 2 positive test results but add to that the 10 false positives and you have up to 12 positive results with no way to know which are the true positive samples. Therefore, you risk giving up to 10 people a false assurance that they have immunity.

This may sound rather hopeless; however, these tests can still be very useful in population testing. If the test is used in a population where the prevalence is higher, e.g. it could be up to 50% in healthcare workers or in people who have/have had symptoms, then the 10% false positive rate has less of an impact. In this situation, the assays can help reassure people on the front line. In simple

terms: the higher the expected prevalence of the infection, the more useful the serology tests or the better the predictive value.

Policy makers want to use these tests to guide their decision to reopen society. If broadly used, the tests could give a valuable view on the prevalence of the disease in particular geographic regions or in areas where the infection rate is expected to be high. They can also help in monitoring the prevalence over time if widespread testing continues. The primary aim is not to prevent further infection but to prepare the healthcare system to ensure it does not become overwhelmed again. It is about moving from crisis mode to maintenance mode.

What has been done in the area of treating the disease, COVID-19, with medication?

COVID-19 could become a seasonal infection. It is highly unlikely to just disappear anytime soon. A recent scientific report in the journal Science suggested that social distancing efforts may need to be extended into 2022 and surveillance measures should be maintained through 2024. Movement restrictions could be lifted without overwhelming the healthcare system **if** treatments and vaccines for COVID-19 are developed, highlighting once again the urgent need for them. Whether it takes one or several years to produce them, the need will still be there.

At the time of our first note, published on March 25th, there was general excitement and enthusiasm regarding the potential use of some old malaria drugs to treat COVID-19. Generic drugs, Hydroxychloroquine and chloroquine are being used in COVID-19 patients, sometime in combination with HIV drugs lopinavir/ritonavir (Kaletra).

We have now seen multiple studies that included hydroxychloroquine and chloroquine. Unfortunately, many of these studies were halted given safety concerns. There is still no conclusive evidence that these drugs provide any benefit to COVID-19 patients. The drugs are still being used in many hospitals because the doctors have no alternative. The initial focus on treatments for COVID-19 centered around drugs such as these malaria treatments because they are already approved for other indications. The problem with these malaria drugs is that the mechanisms of action are unknown, they are not virus-specific, and there are known safety concerns.

There are three types of treatment that have attracted the most excitement so far: antivirals, antibodies and cell therapies.

1. Antivirals:

Hope in this area now rests squarely on the shoulders of Gilead and its antiviral drug Remdesivir. As we anxiously await results from on-going placebo-controlled studies, the drama and intrigue continues. Two large studies being run in China have been halted due to slow enrollment. We do not know if that is because doctors were no longer enthusiastic about the trial or patients were harder to find as the crisis abates in China.

Then last week news was leaked from a hospital in Chicago treating severe COVID-19 patients with Remdesivir. Under normal circumstances, such a leak of data from a single site in a large multi-center study would be disregarded as unethical sensationalism. However, in this new reality, the scraps of news from this single center added billions in valuation to Gilead and heightened speculation and anticipation of a positive read out from the clinical studies. This Chicago hospital recruited 125 people with COVID-19 into Gilead's two Phase 3 clinical trials. 113 of them had severe disease and all were treated with daily infusions of Remdesivir. A video recording of the specialist overseeing the study discussing the results with faculty members was leaked to a medical

journalist, and in a surprising lack of scientific and medical integrity, was published. The journalist obviously could not resist the scoop! In the video the specialist explains that most of the patients had already been discharged and 'only' 2 had died.

Gilead is being more circumspect, as is correct, and looks forward to presenting the full data when available: this could be any day now. The Chicago hospital officially said "*drawing any conclusions at this point is premature and scientifically unsound*." We do not know how severe these patients were and it is important to remember that most patients do recover anyway. Gilead's severe Covid-19 study includes 2,400 participants from 152 different clinical trial sites all over the world. Its second study on moderate COVID-19 includes 1,600 patients in 169 different centers, also all over the world. Well controlled, scientifically evaluated results from the studies will be released very soon and that is what we need to see.

We would caution against expecting Remdesivir to be a magic bullet – anti-viral drug development has often proven difficult in the past. We still do not have effective anti-viral drugs against influenza for example. However, the bar is low for Remdesivir because we do not have anything else to treat COVID-19 right now. There is also the challenge of defining a positive result, or a meaningful and measurable study endpoint: Shortened hospitalization? End of ventilator use? Time to full recovery? These are difficult studies. It may also be the case that this drug works best in newly infected patients – preventing disease progression. There is still much work to be done but we feel confident that these well controlled studies will answer many of these questions.

You would be wrong to think that all our hopes are pinned to this one drug. As of mid-April, there were 211 clinical trials registered to fight COVID-19, with 85 different drugs involved. These trials plan to enroll more than 215,000 participants. A mind-boggling number and reflective of the speed with which this endeavor has taken off. There is a large focus on existing drugs that are already on the market to treat other diseases. Drug repurposing or drug repositioning is a cost-effective way to find new treatment options and researchers can move forward very quickly as the drugs are already tested for safety and approved for other indications by regulatory agencies. Approximately 65% of the ongoing trials include repurposed drugs. These drugs also have the advantage of established manufacturing capacity.

2. Antibodies:

Many and indeed most patients will clear the virus from the upper respiratory tract. Patients experience more severe disease if the infection reaches deep into the lungs. At this point it is often the patients' own immune system which can cause the most lethal problems. The virus may have been cleared by the immune system but not before it triggered a chain reaction resulting in an overactivation of the immune response which can in turn lead to acute respiratory distress syndrome (ARDS) or lung damage; this occurs in up to 20% of COVID-19 cases. According to the WHO, ARDS is the leading cause of death among COVID-19 infected patients. Such an overactive immune response has been characterized by elevated inflammatory marker IL-6 levels and treatment with anti-IL-6 has proven to be effective in other instances of ARDS. Fortunately, there are approved anti-IL6 antibody drugs available, such as Actemra from Roche. Preliminary results from an open-label study in 21 patients with COVID-19 treated with Actemra in China are encouraging. Fever subsided in all patients within the first day of receiving Actemra and oxygen requirements were reduced in 75% of the patients. Controlled clinical studies are underway. Regeneron and Sanofi are also conducting studies with their anti-IL6 compound, Kevzara,

Antibody manufacturer, Regeneron, successfully developed a mixture of antibodies against Ebola. It is now selecting two of these antibodies to use against SARS-CoV-2 and trials are expected to

start very soon. If all goes well, it could be available by early fall for some uses, e.g. for treating extremely sick patients. Eli Lilly, working with a Vancouver startup called AbCellera, has said it hopes to start trials with a similar approach within four months. Vir Biotechnology and Biogen are following a similar path. Antibodies might also be used to prevent infection in the first place, but that could take longer to test in studies.

3. Cell therapies

The innate immune system – a component of a patient's own immune system - is the first line of defense against microbial infections. Cytotoxic lymphocytes such as NK (natural killer) cells and cytotoxic T lymphocytes (CTLs) are necessary for the control of viral infection, and the functional exhaustion of these cells is associated with disease progression. NK cells respond to stress factors to recognize and eliminate cells infected by viruses. US company Celularity received clearance from the FDA to start clinical trials of its stem-cell treatment for COVID-19. The company's therapy, CYNK-001, uses NK cells derived from placental stem cells. Stem cells are un-differentiated cells which under the right conditions can be directed to become any cell type, including in this case NK cells. The idea is that patients who are starting to show symptoms, or who may be at risk for a more severe form of the disease, can be given an infusion of these NK cells to bolster their immune response to the virus. The additional NK cells can help to slow replication of the virus within the body give the patient more time to fight the infection. Cellularity intends to test the treatment in a group of about 86 patients and are optimistic that results could be seen very quickly.

What progress has been made towards developing a vaccine?

According to a recently published report in Nature Drug Discovery, 115 vaccine projects against COVID-19 have been announced and currently 78 of them are confirmed and active, with 5 already at the phase I clinical stage in healthy volunteers. In some ways, developing a vaccine is more straightforward than a potential treatment – you don't need to know as much about the virus. The most widely used vaccine approach targets a protein on the surface of the virus, the so-called spike or S protein. It is known from work on related pathogenic coronaviruses such as SARS-CoV-1 and MERS-CoV that this is a validated approach. The spike protein of the virus mediates attachment of the virus to the cell surface receptors. Targeting the spike protein of the SARS-CoV-1 virus which caused a major health crisis in 2002-2004 lead to the development of several vaccine candidates.

When looking at the large number of companies which have joined the race to develop a vaccine the approaches fall into two camps: traditional technologies and novel technologies. The vaccines attracting the most attention fall into the novel category, the RNA-based vaccines. These technologies offer the promise of rapidity and versatility not seen with conventional approaches. The downside is the potential risk: these novel technologies are unproven. The leader in this field is a company called Moderna which has stated that the potential 'emergency use' of its mRNA-1273 vaccine could be discussed with authorities by the autumn. Most experts put vaccine development out to 12-18 months which would still be an ultra-rapid development timeline for a vaccine.

What is the difference? Traditional vaccines use the virus itself (either dead or made non-infectious) or fragments of the virus (such as the spike protein) to elicit an immune response. Various technologies are used to ensure that the immune response is sufficient to generate long-term immunity to the virus. The novel vaccines however, use the genetic approach: i.e. they take the genetic sequence of the virus and synthesize a DNA or an RNA strand which carries the code for

an essential target protein (such as the spike protein). The idea is that, for example, an RNA vaccine is injected (again there are many approaches to what is in effect very complex technology) into host cells which then take up the RNA and use it as the template to produce large amounts of the viral protein. The viral protein is viewed as foreign by the immune system and triggers the production of antibodies which form the basis of immunity to a possible future infection.

The advantage of the genetic approach is speed. Within 63 days of publication of the SARS-CoV-2 genetic sequence, Moderna had the RNA sequence for its vaccine. There are several other RNA approaches running close, most notably European biotech company BioNTech which is collaborating with Pfizer in its vaccine development program, BNT162. This collaboration could be critical because it is one thing to develop a vaccine in a lab and/or hospital, but scale up and manufacturing are also critical to its rapid dissemination around the world; Pfizer's involvement would make all the difference.

Several Pharma companies are also joining the effort to develop a vaccine. Sanofi and GSK have formed an unprecedented collaboration - Sanofi plans to use technology from GSK to accelerate the development of its experimental vaccine. Most vaccines need an adjuvant to stimulate an immune response. GSK is a specialist in such adjuvants and has developed some of the most powerful ones available – therefore the collaboration between these two pharma giants not only makes sense but increases the likelihood of success.

J&J has taken the unusual move of producing a 30-minute weekly show about its coronavirus vaccine effort to give more clarity on how Pharma works. J&J has its own vaccine technology and manufacturing capacity. The company has stated that its facility in Leiden, the Netherlands, could produce about 300 million doses per year and it is also establishing a new capacity in the US.

With approximately 115 vaccine development programs ongoing and several at or close to being in clinical development, we think that a vaccine can and will be produced against SARS-CoV-2. The bigger question is how long will that take. Moderna and BioNTech lead the way in developing novel genetic based vaccines and have the potential to be the first vaccines available. However, the very novelty of the approach introduces additional risks to safety, efficacy and manufacturing. For the more traditional vaccines, we have a large body of information and experience and there is manufacturing capacity already in place.

The potency of a vaccine can be assessed by its ability to generate neutralizing antibodies. The idea being that if a vaccinated individual is infected with the virus – it will be quickly cleared by the neutralizing antibodies generated by the vaccine. It will also be critical to know the duration of protection provided by the vaccine. Vaccines are given to the most vulnerable in society, the elderly and those with underlying health issues. A vaccine needs to be VERY safe to avoid inadvertently doing more harm than good. What we can say at this point is that the best and most experienced people, including research groups, companies, regulatory agencies, funding agencies and more, are throwing everything they have at this problem. The industry is collaborating and truly pulling together like never before to develop and produce a safe, effective vaccine as soon as possible. As to how long it will take – well we need a bit of luck that the first efforts are successful. At this stage we can be hopeful that at least an initial vaccine will be available some time in 2021.

Conclusion:

Five weeks have passed since our first note and the fight against SARS-CoV-2 is advancing on all fronts. Diagnostics are now widely available – perhaps they are not perfect but broad testing will inform decisions as to when and how we re-open society. The scale of drug and therapeutic

development is staggering and the speed is unprecedented. Everything, from trawling through the banks of molecules at pharma and biotech companies, to repurposing existing drugs, to using cell therapy, is being thrown at this problem and companies and scientists are collaborating like never before. The scope of vaccine development is also expanding from traditional approaches to cutting edge technologies; it is more a question of “when” and not “if” we will have a vaccine for this disease.

We will close where we started in the introduction which is to say that it is people, and how they have responded to this crisis, which has flattened the curve and prevented an even worse disaster in many countries.

We are now better prepared for what comes next.

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