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What Could Get Us Out of the COVID-19 Pandemic Beyond Current Measures?

Treatments as a bridge to vaccines and serological testing.

I have been thinking through what could get us out of the COVID-19 pandemic beyond current measures. Treatments as a bridge to vaccines as well as broad serological testing are near-term events that could move the U.S. into the next phase toward ultimate recovery.

While this note does not answer the burning question as to when the outbreak will peak in the U.S., we do note that day-over-day patient growth rates are holding steady in New York State and New York City at 13.8% and 11%, respectively, a sign that perhaps we could begin to grow at a slower rate in the coming days. We think the way toward ultimate recovery is by finding a treatment for those afflicted and identifying those who perhaps have been infected yet had a largely asymptomatic course of disease, and hence some type of immunity. To this end, we offer the following:

Serological testing: Data out of a Chinese group shows solid results on antibody development in COVID-19 patients. Last Thursday, we sent out an update on potential serological testing in the U.S. with Henry Schein promising to distribute "hundreds of thousands" of point-of-care tests to physicians' offices by the end of March or early April. While we still are a bit concerned about the potential for false positives for a test that has not been FDA-validated, a report out of China last night further supports that antibody titers against SARSCoV2 begin around day 7 (~40% positive for antibodies at low levels) and peak beginning day 15 though day 39 post infection with 93% of COVID-19 positive patients seroconverting with a healthy mix of subtypes IgM & IgG. The test used in this study is one from Beijing Wantau Biological Pharmacy Enterprise, a private Chinese firm.

Academics and private companies are getting involved. Over the weekend, we found several articles pointing toward a plethora of academic labs making progress on a SARSCoV2 serological test with Mount Sinai publishing their data, and Tulane University and my alma mater Rockefeller University taking an all-hands-on-deck approach to developing a test. Additionally, we have confirmed that the commercial reference labs Quest Diagnostics and OpkoHealth's Bioreference Labs are actively working, as are smaller diagnostics companies such as Biomedomics (the company from which the U.K. bought 3.5 million tests), Phamatech, Nirmidas and Genalyte, the latter San Diego company claiming 6,000 tests per day on their MAVERICK platform, although final specs on the antibody tests are still being worked out.

Our one cautionary note is the risk of false positives on antibody serological tests for antibodies that are coronavirus antibodies however may be raised to the less virulent strains such as OC43, NL63, 229E & HKU-1, which have been circulating since the early 2000s and show limited if any clinical sequelae. We need confirmation of specificity to SARSCoV2 (and not SARScoV1, either) proteins in order to be convinced that widespread serological testing will be accurate and allow the U.S. to move to the next phase in COVID-19 recovery.

Treatment Overview: A chart is worth a thousand words, so below is an overview of antivirals in development as well as antibodies/plasma transfer programs, all of which intend to report out data in the next 1 – 2 months. Should any or several of these programs be successful, we think it could be the trigger that signals the beginning of the end of the COVID-19 nightmare for our country. Note that our opinion on each program is included at the bottom of the charts. While writing this note, we were notified by one of our portfolio management teams of a press release out of France, stating the "the French government has officially sanctioned prescriptions of chloroquine to treat certain Covid-19 patients." We are cautiously optimistic on hydroxychloroquine as well as Remdesivir, and have renewed hope for an old Hepatitis C drug called danoprevir, but, while we keep looking for more information, we currently only have data from one small Chinese study.

Anti-Virals					
Company	Remdesivr Gilead	Favipiravir FujiFilm Toyama	Hydroxychloroqine Generic	Lopinavir + Ritonavir Abbvie/Generic	Danoprevir Ascletis Pharma
Positives	Direct antiviral activity Anecdotal evidence of clinical activity Respected anti-viral company	Direct antiviral Oral dosing advantage Two studies showing hints of efficacy	Anti-Malaria drug Generic and orally dosed 3-pronged approach to viral control/ inflammation Anecdotal evidence of efficacy	HIV protease inhibitor with a boosting agent	HCV-NS3 protease inhibitor with a booster One positive study in Chinese patients with robust activity
Negatives	IV dosing restricts use, Must be used early in infection Liver toxicity issues	Needs to be dose early in infection Concerns regarding dosing & safety	Safety (ocular, Qtc) Questions regarding data out of China which states efficacy but without data	Failed study vs Favipiravir however hints of activity	one study in 11 patients, no control group
Expected Clinical trials	Chinese trial readouts in early to mid April Gilead trials in May	Combination trial with an anti-IL6 antibody (Actemra) in June 2020	NY State 5,000 patient study reads out in early May 2020 Prophylaxis study in July	Study vs Hydroxychloroquine, data in May 2020	????
NB opinion	Cautious optimism for use in most severe patients who are hospitalized	Less inclined based on mixed data/ doses used, South Korea passed	Cautious optimism, drug used across most NYC hospitals, mechanism makes sense	We question how similar the HIV protease is to the SARS CoV2 protease	We are intrigued, think it inhibits the protease differently than the failed Lopinavir study

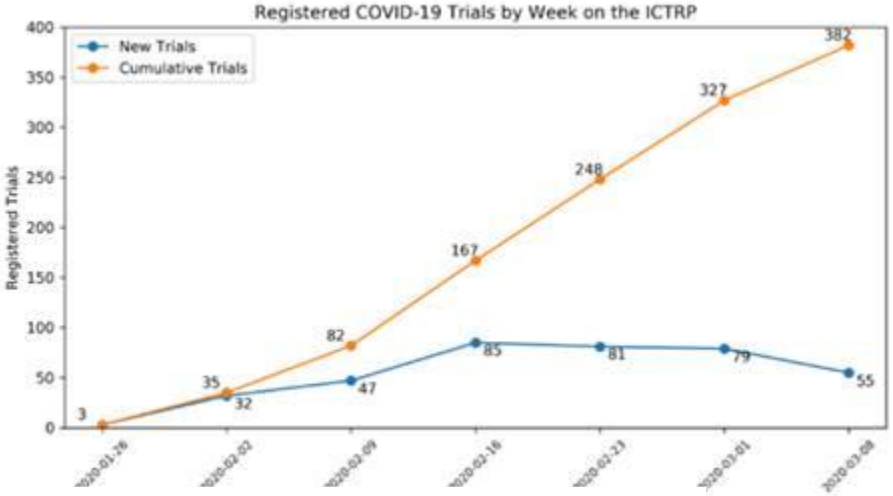
Source: clintrials.gov, Neuberger Berman data and research, Wolfe research data.

Regarding therapeutics, we are more optimistic for engineered antibodies, as supported by the Regeneron approach (highly specific, potent and safe) but recognize the benefits of convalescent plasma. We also highlight that engineered antibodies could be used as a prophylactic with passive immunity transfer to healthcare workers and first responders, hopefully as early as late fall.

Antibodies					
Company	Engineered Ab Regeneron	Plasma IgG FujiFilm Toyama	Actemra Roche	Kevzara Regeneron	Soliris Alexion
Positives	Antibody attacks the virus spike protein 3-4 Antibodies per infusion to defend against mutation	Treatment or Prophylaxis Was employed during the SARS outbreak	Anti-IL-6 antibody globally marketed for Rheumatoid Arthritis, acts on inflammation or Cyotkine storm in lungs of COVID19 patients		Evidence that a marker of complement activation called LDH is elevated in severe COVID19 patients
Negatives	IV dosing restricts use Expensive to manufacture	Requires pooling plasma from COVID19 patients who have recovered	We really do not see any given large quantities currently available, known safety profile		Soliris is IV infused every 2 weeks, we see more utility for Ultomiris IV infused every 2 months
Expected Clinical trials	Studies begin in ealry summer, REGN has identified ~300 neutralizing antibodies	First large study of 100 patients with data in May/June 2020 (Wuhan, Shanghai)	5 trials ongoing, REGN study in NY state read out in early May, Academic trials report in late April/May, Combination with anti-virals early June		One clinical trial/expanded access program enrolling patients now
NB opinion	Optimistic given REGN's track record with Ebola EB3, HC workers use as passive immunity	Encourging results from previous epidemics (H1N1 & SARS-CoV2) keeps us optimistic	Confidence rising for a role in more severe cases in lowering mortality stemming from cytokine release syndrome in COVID 19 patients		Complement has known to play a role in overactivation of the immune system however no trial data to date

Source: clintrials.gov, Neuberger Berman data and research, Wolfe research data.

We plan to cover a select group of the > 40 vaccine trials in our next note, but will leave you with a simple chart that captures the trials that are being done to reach the goal of eliminating COVID-19, or at the very least help make it a treatable illness should it linger throughout the year.



Source: https://www.cebm.net/covid-19/registered-trials-and-analysis/

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For more information on COVID-19, please refer to the Center for Disease Control and Prevention at cdc.gov.

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