APRIL 2020

PERSPECTIVES ON CORONAVIRUS

LAZARD

Agenda

Executive Summary – *The Near-term Outlook*

Lazard has closely studied the SARS-CoV-2 pandemic, including its growth trajectory, its public health and economic implications, responses from policymakers and therapeutics developments. We have developed five scenarios that bookend the range of likely trajectories and draw conclusions on the key developments that will determine the ultimate course of the disease

1

Forecasting Potential Scenarios

- **Epidemiological modeling is a significant challenge under the best circumstances as evidenced by the number of conflicting figures circulating in the popular press**
- **Modeling the SARS-CoV-2 pandemic is particularly difficult given:**
  - Biological unknowns (e.g., rate of transmission, seasonality, degree/duration of acquired immunity, ability of children/pets/asymptomatic people to spread disease)
  - Results of socio-political efforts to mitigate transmission (i.e., social distancing)
  - Impact of therapeutic developments (e.g., effect of supportive care improvements on mortality, antiviral effects on hospitalization / transmission)
- **Based on the above inputs, we have developed five scenarios that bookend the range of likely trajectories for the pandemic (e.g., by sensitizing the degree and duration of social distancing measures employed)**
- **Among other factors, forecasts highlight the likely need to maintain social distancing for the foreseeable future in order to control hospitalizations, absent availability of an effective therapeutic and/or strong warm-weather effects**

Key Developments to Watch

- **We see five key developments as significant inflection points in the near term for the disease and its spread:**
  a) Adherence to and duration of the lockdown in Italy
  b) Clinical trials of drugs for treating COVID-19 (see subsequent page for additional details)
  c) The virus's trajectory in warmer climates (e.g., South America and SE Asia)
  d) Possible resurgence of the virus in China and South Korea
  e) Potential improvements in the accuracy and availability of viral testing

Political & Economic Implications

- **Monetary policy authorities are launching significant interventions to stem economic impacts of the pandemic; however, their effects are likely to be muted**
  - BARDA has begun working with industry to scale up capital and other resources to accelerate the discovery, development and production of therapeutics
- **Fiscal policy interventions being contemplated could have a more significant effect but face major hurdles**
- **Political science research and prediction markets alike indicate that outcomes in the 2020 U.S. general election, among other elections around the world, will be tightly coupled to the depth and duration of economic contraction**

Executive Summary – *The Evolving Treatment Landscape*

The development of effective therapeutics could have the most profound impact on the course of the disease while also presenting a less economically injurious alternative to policy measures currently being pursued; unfortunately, vaccines will not be available in the near-term and there are significant challenges for antivirals

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Strategies for Treating SARS-CoV-2	• **In the following pages, we have outlined key treatment strategies, promising therapeutics undergoing development for SARS-CoV-2, and timing for when these treatments may become available** • **Various treatment strategies are being developed to address the natural progression of the COVID-19:** – Virus uptake: Vaccines (e.g., Moderna), antibodies (e.g., Regeneron) and small molecules (e.g., Chloroquine) that prevent infection – Viral replication: Small molecules designed to interrupt SARS-CoV-2's ability to replicate in the host (e.g., Gilead's remdesivir and Chloroquine) – Immune response: Drugs designed to mitigate hyperactive immune responses (e.g., Roche's Actemra) and offer supportive care (e.g., Bellerophon's INOpulse) • **Vaccines may be the most effective tool for combatting the virus in certain transmission scenarios, but out of current treatment options, they will take the longest to develop, likely becoming available in 18+ months** – As such, both repurposed and novel therapies for supportive care, inhibiting viral replication and preventing viral uptake will be the most critical in the short-term
The Evolving Landscape	• **Preclinical and emerging evidence for several antivirals appears promising, but there have been flaws in trial design that prevent a definitive conclusion on efficacy** – To date, chloroquine has reported the most clinical results. While many of the trials have had issues with size and design, recent results from a randomized trial (n=62) conducted in Wuhan showed encouraging results with statistically significant improvements on various clinical endpoints including duration of cough and fever and improvement in pneumonia. Chloroquine has a unique mechanism that could hold promise as an oral prophylactic but has safety issues and drug-drug interactions that could preclude widespread use – The most compelling option, based on preclinical work, is Gilead's remdesivir, with high-quality data expected in early April; readouts from favipiravir may also point to positive readthrough for remdesivir given the latter has a more promising preclinical profile • Unfortunately, remdesivir may have limited benefit at a population level, as it is administered intravenously and therefore likely to only benefit hospitalized patients
Challenges and Other Considerations	• **Despite promising advances there are numerous challenges for therapeutic development during a pandemic** – Conducting well-designed, comparable studies across drugs in a way that is safe for patients and providers – Challenges with diagnostics limiting effectiveness of interventions because patients are diagnosed too late – Market access challenges given uncertain regulatory pathways and off-label use

Executive Summary – *Objectives of Diagnostic Testing*

The objective of diagnostic testing varies at different stages of a pandemic, evolving from a tool for containment (e.g., rapidly identifying infected individuals to drive contact tracing) to a tool for surveillance. As the pandemic progresses, diagnostics and serological antibody testing begin to play a more important role in informing mitigation policy and eventually become a surveillance tool

3

Containment

- **Rapid, widespread testing (as in S. Korea) is critical for early-stage of pandemic**
  - Facilitates contact tracing and allows for isolation of contagious individuals
- **CDC should rapidly develop and validate protocols with clear EUA guidelines to facilitate scaling national and local laboratory capacity**
  - Game-changing launch of Abbott's rapid, point-of-care SARS-CoV-2 test for its ID NOW system, originally developed to test for Strep and the flu in POC settings, which has the largest installed base of any molecular POC testing platform in the U.S.

Mitigation

- **With widespread transmission, monitoring infection rates is critical for informing policy decisions (e.g., when to end shelter-at-home orders)**
  - Testing a representative sample of the population for serological antibodies can inform level of acquired immunity in the population (success shown in limited applications in Italy)
- **Drive-thru, point-of-care and at-home testing become important tools for monitoring rate of infection while avoiding transmission at outpatient testing sites**

Surveillance

- **Much like initial stage of the pandemic, rapid testing and contact tracing critical for avoiding resurgence**
  - Point-of-care diagnostics at the level of PCPs become important tool for quickly identifying and isolating infections in the community
- **Periodic serological antibody testing critical for monitoring population-level immunity (quality and duration)**
  - Particularly important given weak/short-lived immunity observed with SARS and MERS

Key Learnings for Pandemic Preparedness

- **CDC must be prepared to quickly scale diagnostic capabilities with clear guidelines for EUA**
  - Supply chain issues should be addressed early (e.g., swabs, reagents)
  - Testing criteria should be relatively inclusive
- **Contact tracing can be augmented through digital / AI tools that can help with early containment**
- **Avoiding transmission by separating testing from hospitals where infected individuals are treated and reducing contact between providers and patients is critical**
- **Developing antibody testing is as critical as infection diagnostics and should be rapidly developed / deployed**

Executive Summary – *Additional Implications and Analyses to Come*

Beyond the likely forecasts for the disease and therapeutic developments, the pandemic is already having an impact on the economy, healthcare sector and M&A trends; we examine preliminary implications below with subsequent analyses to come

Perspectives on Policy Responses

- **Emerging consensus among policymakers around the world that direct business aid will be necessary to ameliorate lasting economic damage from the crisis**
- **Such tools are largely unprecedented in the modern era—will entail experimentation and heterogeneity**
- **What is the range of design parameters for proposals under consideration?**
- **What interventions have country officials proposed?**
- **How are academics and independent analysts positioning their proposals?**

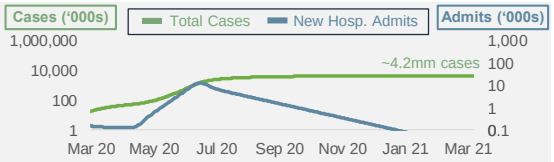
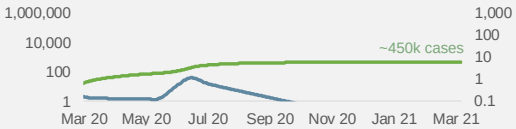
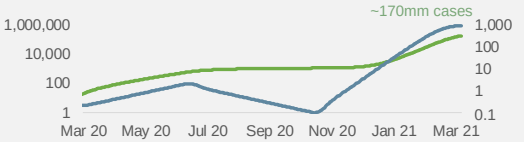
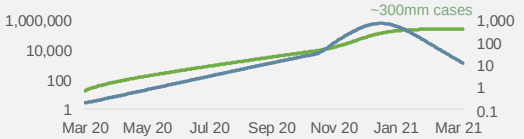
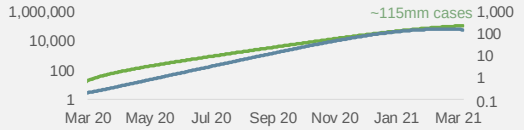
Operational Implications for Healthcare Sector

- **The entire value chain is already being impacted by the pandemic:**
  - **R&D:** Clinical trials are being put on hold
  - **Manufacturing:** Supply chain disruptions and delayed inspections are creating shortages
  - **Commercial:** Face-to-face physician detailing is on hold
  - **Care delivery:** Providers and facilities are diverted to COVID-19 treatment
- **How will these disruptions impact the long-term operations and intrinsic value of companies?**

Impact on M&A

- **Valuations have decreased substantially since the outbreak**
- **Equity markets are closed with funding rounds delayed or cancelled**
- **Operational disruptions are impacting intrinsic value**
- **What will be the overall impact on M&A?**
  - Will there be differentiated impact across segments and company profiles
  - How will dynamics play out over time?
  - What are the specific considerations for deal execution
- **How should companies be proactively preparing?**

1 COVID-19 Outlook: Potential Scenarios

	Brief Description	Key Parameters: Social Distancing Efficacy	Social Distancing Duration	Effective Antiviral Therapy[1]	Seasonality (Based on Northern Hemisphere)	Fall Resurgence	Illustrative U.S. Projected Cumulative Cases and New Hospital Admits
Scenario 1	Early termination of social distancing—in part due to antiviral therapy	High	May	May	Yes	No	
Scenario 2	Delayed availability of antiviral therapy; social distancing extended to summer	High	June	August	Yes	No	
Scenario 3	Seasonality offset by fall resurgence; antiviral therapy delayed until fall with social distancing maintained	Medium	November	November	Yes	Yes	
Scenario 4	Delays for antiviral therapy and no seasonal protection; social distancing in place until fall	Medium	November	November	No	N/A	
Scenario 5	No antiviral therapy or seasonal protection; social distancing continued year-round	Medium	Through March 2021	Never	No	N/A	

Economic impact principally driven by duration of social distancing, though also related to other factors

Source: American Hospital Association.

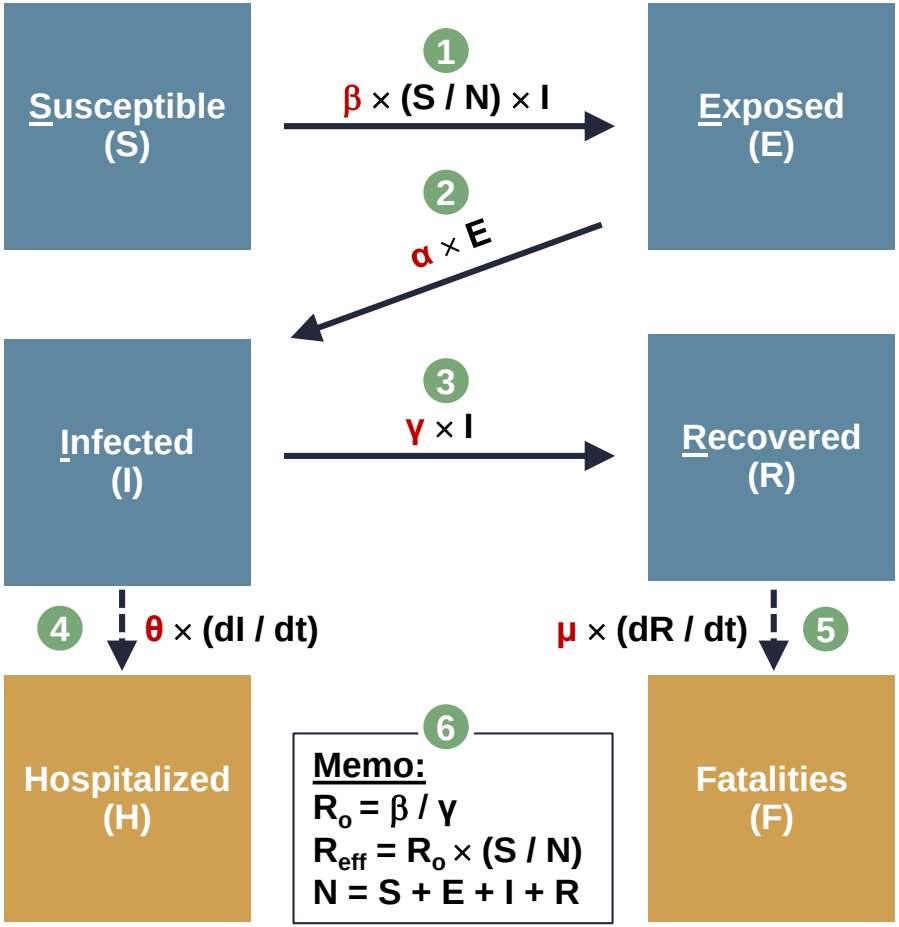
Note: Projected cases, hospitalizations and fatalities based on SEIR model. Assumed incubation period of one week; infection time course of 12 days. Baseline R_0 of 3, with R_0 of ~1 under high-effectiveness social distancing, of ~1.5 under medium-effectiveness social distancing, and of ~0.5 during the summer (defined as July 1 through October 30). R_0 on a two-week rolling geometric mean to account for transitions. Baseline case fatality rate of 1%; 0.1% fatality rate with effective antiviral therapy. 15% of infections assumed to result in hospitalizations.

1 Defined as therapy sufficiently effective so as to change popular psychology around the pandemic and allow for return to normal patterns of social and economic behavior.

1 COVID-19 Modeling Methodology

Lazard's COVID-19 scenario forecasts are derived from an internal SEIR model, based on a "workhorse" framework in the epidemiological literature for forecasting viral outbreaks. The model tracks four main groups: the population susceptible to the virus, S; the population exposed to the virus but not yet manifesting infection, E; the infected population, I; and the population for whom the disease has run its

SEIR Model Framework



Description and Observations

- **Model parameters are fitted to COVID-19 disease dynamics based on empirical data from China, Italy, and other regions**
- **Key flows between the groups:**

1. **Susceptible individuals' exposure to the virus is based on the average number of people an exposed person transmits the disease to each day (β), mediated by the impact of herd immunity (S/N)**
   - β is sensitized to account for social distancing measures and the impact of seasonal transmission changes
2. **Exposed individuals become fully infected once the average incubation period of the disease (1/α, or ~7 days) is complete**
3. **Individuals "recover" from the disease once it runs its average time course (1/γ, or ~12 days)**
4. **A subset (θ, or ~15%) of newly infected patients become hospitalized for the duration of their infection**
5. **A subset (μ , or ~1%) of "recovering" patients represent mortalities from the disease**
   - μ is sensitized to account for the availability of effective antiviral therapies
6. **R_o is a key indicator representing how many people each COVID-19 case on average infects over the disease duration; if immunized share of the population exceeds 1 – 1/R_o, herd immunity is strong enough to contain the disease**

- **Flows are modeled on a daily basis over 12 months**

1 COVID-19 Modeling Methodology (cont'd)

The SEIR model rests on key implicit assumptions embedded in its framework, beyond the listed parameters

	Key Assumptions
Susceptible Population	• **Model based on national U.S. population, including adults and children** • **Homogenous population, i.e. tracking population-average effects** • **Steady-state population with births and deaths from other causes canceling out** • **All individuals assumed to have baseline susceptibility to virus; no innate immunity prior to infection** • **No vaccine or prophylactic available over duration of model** • **No reinfection risk, i.e. "recovered" population assumed to be no longer susceptible**
Transmissibility	• **"Even" mixing of population; hospitalized individuals continue to transmit disease at same rate** • **Contact with exposed (but not fully infected) individuals does not result in disease transmission** • **Transmission rate not affected by therapeutic availability** • **Disease characteristics held constant, i.e. no clinically meaningful mutation of virus in next 12 months** • **Infections represent actual case count rather than reported case count**
Disease Severity	• **Incubation period and time course of the disease held constant** • **Constant fatality rate, absent sensitization from therapeutic availability** – Individuals not hospitalized assumed to have ~0% fatality rate – Saturation of national hospital bed capacity (and potential impact on fatalities) not explicitly modeled • **Hospitalization rate not mediated by therapeutic availability**

1 Key Developments to Watch

	Adherence to and Duration of Lockdown in Italy	Pivotal Trials of Antiviral Drugs	Case Trajectory in South America & Southeast Asia	Possible Resurgence in China & South Korea	Improvements in Accuracy and Availability of Testing
Considerations	• Italy was first Western country to impose large-scale lockdown • Economic burden and social costs of Italy's lockdown could result in fatigue and drop-off in adherence, particularly given that virus is asymptomatic or mild in most cases • Challenging to handicap likelihood of fatigue given unprecedented circumstances • Fatigue may be a more significant issue in the U.S. vs. Italy	• An effective antiviral could take much of the fatality risk "off the table," allowing phase-out of social distancing measures • Lead antiviral in development is Gilead's remdesivir; interim results from Chinese trials (~750 enrollees) as early as the end of March • Other marketed drugs (e.g., chloroquine) being tested and used off-label; efficacy uncertain • Vaccine timeline seen as ~18+ months to wide-scale availability	• Recent data from China suggests that COVID's transmissibility is lower in warmer cities; if data is borne out, it would be cut in half by July/ August in the U.S. • Cross-country data has been mixed so far: e.g., Singapore vs. Australia • As disease spreads (or does not) in South America and Southeast Asia (e.g., Malaysia) we will have a much better sense of its seasonality	• Ample reason to believe that the virus is likely to resurge even after social distancing measures stem case growth, if indeed they do, once these measures are lifted • Similar behavior was seen with the 2009 swine flu, SARS and the 1918 Spanish Flu (albeit some seasonality with flu) • Since disease has already peaked in China and South Korea, these will provide advance warning of potential resurgence	• RNA test-kit shortages, particularly in US and Europe, are hindering disease management; shortages may abate • Development and proliferation of serology (antibody) test would enable identification of immune population and assessment of reinfection risk • Symptom-based tests (e.g., temperature) challenged by high rates of asymptomatic transmission • As testing expands, mortality may be adjusted downward (as in the 2009 swine flu)
Parameters Affected	• **Social distancing efficacy and duration**	• **Availability of antiviral therapy** • **Social distancing duration**	• **Seasonality** • **Social distancing duration**	• **Resurgence** • **Social distancing duration**	• **Mortality rate** • **Social distancing duration**

1 Additional Factors for Consideration

Health and Medical Factors

- ? Sensitivity and specificity of COVID diagnostic tests (temperature, PCR, etc.), particularly over time course of disease
- ? Degree to which the virus can reinfect those who have ostensibly become immune (e.g., following mutation); viral genome appears stable thus far
- ? Degree to which asymptomatic transmission is a driver
- ? Potential for children, pets, etc. to be major carriers
- ? Concurrent flu season and other diseases that could further tax strained health system
- ? State budgetary cuts to public health programs as local tax revenue falls, absent federal relief

Economic Factors

- ? Magnitude and form of monetary and fiscal policy response
- ? Geopolitical interventions from state and non-state actors (including, e.g., cyberattacks)
- ? Degree of social unrest or upheaval
- ? Disruptions to key elements of supply chain
- ? Credit crunch and/or instability of banking system
- ? Natural disasters and other shocks
- ? Sovereign debt crises from widening risk premia

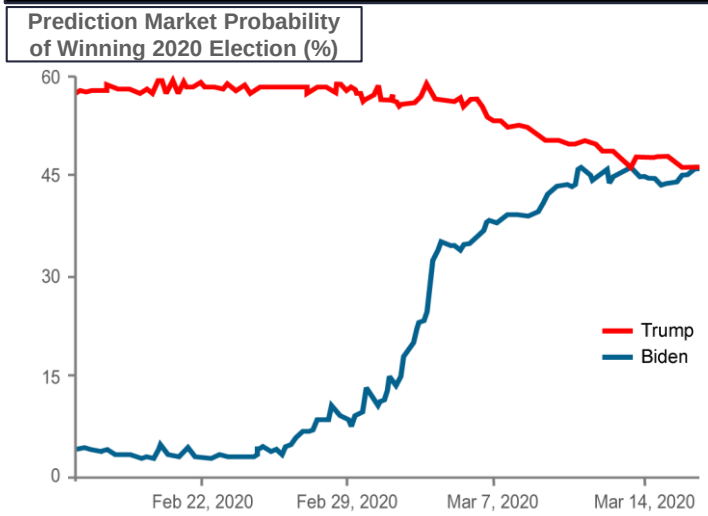
Further Detail on Following Page

1 Policy Response and Electoral Consequences

Overview of Proposed Policy Responses

		Key Provisions	Selected Questions
Monetary Policy	Fed	• Near-zero fed funds rate • $700+ bn QE, including corporate credit and other new 13(3) facilities • $1.5 trillion intervention in repos • Significant potential expansion in asset purchases via fiscal package	? Efficacy given real-economy challenges ? Impact of yield curve flattening and negative real rates on banks ? Credibility of traditional central bank action given persistently low target rates and inflation
	ECB	• Expanded asset purchases • Maintenance of benchmark overnight interest rate at -0.5% • TLTRO facility borrowing rate for banks reduced to -0.75%	
Fiscal Policy	US	• ~$2 trillion stimulus package passed and signed into law by President Trump on March 27, 2020 • Provisions to include direct business lending for small, medium, and large enterprises; expanded unemployment insurance; paid sick leave; direct rebate checks; and others	? Inside lag ? Impact of legislative gridlock ? Efficacy given size of demand shortfall ? Appetite for direct business aid and bankruptcy avoidance vs. conventional economic tools (e.g., cash transfers to individuals) ? Degree to which central-government aid is offset by regional / local budget cuts
	Europe	• German state bank pledged €550bn in emergency lending to companies, with additional fiscal measures forthcoming • France initiating €300bn of state loan guarantees for businesses • Variety of other actions by European leaders and the EC	

Considerations for U.S. Electoral Implications



- **Prediction markets are pricing in significant reduction in Trump reelection prospects due to coronavirus management and recession risk—but remains a 50/50 proposition**
- **Political science models indicate that economic trends play an outsize role in determining reelection prospects:** incumbent president not reelected five of the last seven times there was a recession within two years of the election
- **Cities hardest-hit by coronavirus so far are primarily coastal, Democratic-leaning; recession would have countrywide implications**

Source: Congress.gov, Betfair, and PredictIt.

1 Sources of Economic Vulnerability – Examples

Potential Disruptions to Key U.S. Business "Clusters"

Industry	Key Geographies
Agriculture	Fresno, CA
Livestock	Fayetteville, AR
Fishing	Anchorage, AK
Financial Markets	New York, NY Chicago, IL
Credit Card Processing	Omaha, NE
Insurance	Hartford, CT
Defense Contracting and Aerospace	Seattle, WA Wichita, KS

Potential Labor Market Dislocations

Category	Examples
Healthcare	• Physicians and nurses • Home health workers • Lab and radiology technicians
Mail, Shipping and Third-Party Logistics	• FedEx and UPS drivers • USPS workers
Food Delivery	• Couriers/drivers
Transportation	• Cab drivers • Rideshare services
Judicial and Regulatory	• Court staff • SEC staff
Security and Law Enforcement	• Police officers • Firefighters • Private security services
Maintenance and Infrastructure	• Plumbers • Electricians • Civil engineers
Local Media	• Reporters and news staff

Source: Harvard Business School, Institute for Strategy & Competitiveness.

1 A Roadmap to U.S. Coronavirus Response and Recovery

Below we illustrate a potential roadmap for evolving U.S. policy from strict efforts meant to slow the spread to the development of vaccines and other therapeutics that allow for an eventual return to normalcy

	Phase 1: Slow the Spread[1]	Phase 2: Reopen, State by State	Phase 3: Establish Protection then Lift All Restrictions	Phase 4: Rebuild our Readiness for the Next Pandemic
Goals	• Slow transmission of SARS-CoV-2 by reducing the effective reproduction number of infections • Increase capacity to test everyone with symptoms and their close contacts • Ensure the healthcare system has the capacity to safely treat both COVID-19 patients and others requiring care	• Lift strict physical distancing measures in a concerted and careful fashion • Allow the vast majority of businesses and schools to open • Continue to control SARS-CoV-2 transmission to avoid reversion to phase 1	• Prevent infection • Treat the infected early to prevent bad outcomes • Provide a prophylaxis for those exposed to improve outcomes • In the case of a vaccine, build population-level immunity to the virus in order to reduce illness and death and stop or greatly slow spread • Enable the lifting of all physical distancing measures	• **Develop vaccines for novel viruses in months, not years** • **Modernize and fortify the U.S. healthcare system** • **Establish a national infectious disease forecasting center** • **Develop plan for coordinated execution of response for future pandemics**
Steps	• Maintain physical distancing • Increase diagnostic testing capacity and build data infrastructure for rapid sharing of results • Ensure healthcare system functions • Increase supply of PPE • Implement comprehensive COVID-19 surveillance systems • Scale contact tracing and quarantine • Encourage public to wear masks	• Implement care-based interventions • Begin to relax physical distancing measures • Special care for vulnerable populations • Accelerate the development of therapeutics • Identify those who are immune	• Vaccine or therapeutic production – Vaccine or therapeutic prioritization (when supply is limited) – Mass vaccination or therapeutic distribution (when supply Is abundant) • Global vaccine scale-up and vaccination • Serological surveys to determine population immunity	
Triggers for Moving to the Next Phase	• A state reports a sustained reduction in cases for at least 14 days (i.e., one incubation period) • Local hospitals are safely able to treat all patients without resorting to crisis standards of care • Capacity exists in the state to test all people with COVID-19 symptoms • Capacity to monitor all confirmed cases and their contacts	• A vaccine has been developed, has been tested for safety and efficacy, and receives FDA emergency use authorization **OR** • There are non-vaccine therapeutic options that can be used for preventive care or help rescue very sick patients	• As soon as a vaccine has been proven safe and effective, the U.S. government should work with industry to begin planning for mass manufacturing, distribution, and administration	

Source: Scott Gottlieb et al. American Enterprise Institute. March 2020.
1 Current phase.

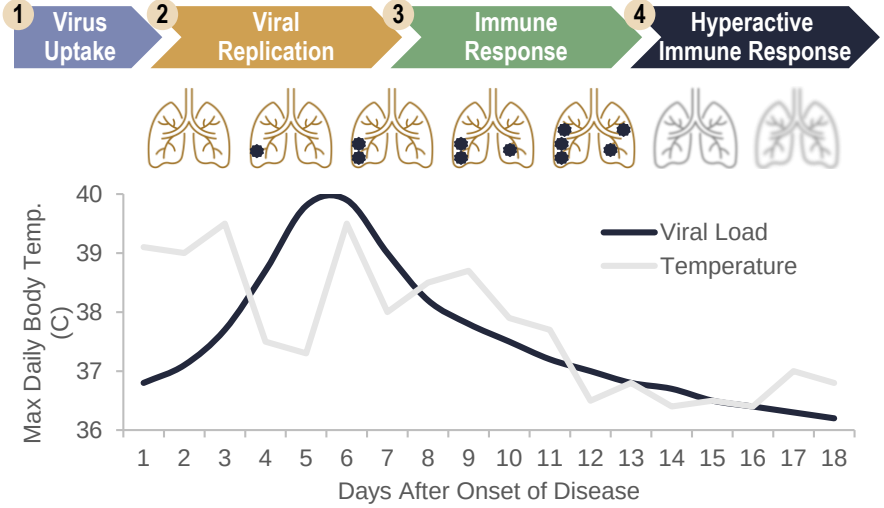
1 Potential for a "New Normal"

- **The most important activities we undertake today—economic and social—are done largely in person**
- **Foundational social functions are primarily conducted face-to-face: business meetings, medical care, education and government services (e.g., jury duty) to name a few**
  - Less than 5% of Americans primarily work from home (St. Louis Fed data)
  - More than eight in ten executives prefer in-person meetings to virtual contact (per Hilton)
- **Preference for in-person interaction also applies to discretionary services and experience: retail experiences, sporting events, dining, fitness, general social interaction, etc.**
  - Only about 11% of retail sales are conducted via e-commerce—a category particularly amenable to virtual interaction (Census data)
- **Key question: at what point does mandatory social distancing cause this to flip? In other words, when do we shift toward another equilibrium where virtual interaction across these domains is more common? This could include:**
  - Reduced travel, including for business
  - Significant increase in virtual health and care
  - Virtual forums become default social space (e.g., as we are seeing with Fortnite and other platforms generationally)
  - Growth in e-sports and virtualization of professional sports
- **Additional dimensions of potential change:**
  - Global supply chain resiliency (and planned redundancies)
  - Norms and practices around employee paid sick leave
  - Secular decline in particular types of consumption (e.g., cruise lines)

2 Potential Strategies to Develop Therapeutics for SARS-CoV-2

While developing an effective vaccine would be the ideal treatment solution, alternative strategies are in development that aim to prevent infection or reduce viral load, which can cause a severe immune response that leads to acute respiratory distress syndrome and fatality in some patients

Course of Disease



1. R_0 of 2.2[1] with persistence of up to 72 hours on hard surfaces and 3 hours as an aerosol[2]
2. Viral replication happens exponentially with symptom presentation at a median of ~5 days[3] following exposure and viral peak at 7+ days post exposure
3. As viremia increases immune response is activated with 90% of cases presenting with fever
4. Many cases showing "ground-glass" in peripheral lung CT scans and can progress to acute respiratory distress syndrome (ARDS)[4] and secondary pulmonary infection / pneumonia leading to mortality in ~2% of cases[4]

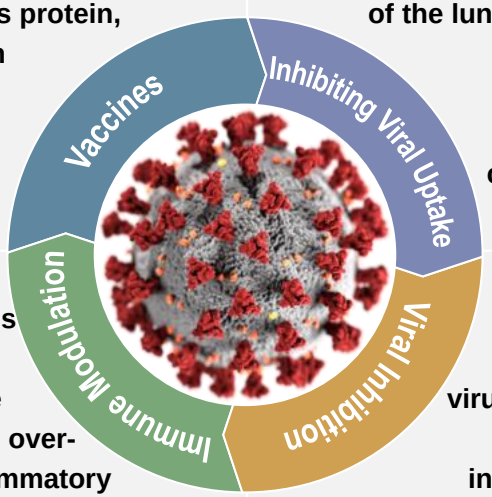
Strategies for Treatment

Vaccines

Vaccines induce adaptive immunity by introducing a coronavirus viral antigen (i.e., spike protein) either through an esophagus protein, mRNA (which produces the protein) or attenuated virus

Inhibiting Viral Uptake

Coronaviruses bind to target cells through angiotensin-converting enzyme 2 (ACE2), expressed by epithelial cells of the lung. Preventing binding with neutralizing antibodies could prevent infection[5,6]



Immune Modulation

Many of the most injurious symptoms of COVID-19 are caused by an over-reactive inflammatory response in the lungs. Interfering with immune cytokines (e.g., IL-6) could mitigate the most severe symptoms[7]

Viral Inhibition

Antivirals interrupt the ability of the virus to replicate primarily by interfering with replication enzymes (e.g., RNA polymerase)

1 Cascella et al. NIH. January 2020.
2 van Doremalen et al. NEJM. March 2020.
3 Lauer et al. Annals of Internal Medicine. March 2020.
4 Xu et al. Lancet. February 2020.
5 Fang et al. Lancet Respiratory Medicine. March 2020.
6 Hough, Jack. Barron's. March 2020.
7 Mehta et al. Lancet. March 2020.

2 Overview of the Developing Treatment Paradigm

The goals of treatment vary by stage of intervention and mechanism. A successful prophylactic treatment would largely obviate the need for therapies aimed at reducing viral load or dampening the immune response but appear to be the farthest from being viable. In the intermediate term, there are various therapies that could mitigate the most injurious manifestations of COVID-19 and are expected to have clinical trial data in the near term

	Vaccination	Inhibit Uptake	Viral Inhibition	Immune Modulation/ Supportive Therapy
Commentary	? **Spike proteins are the element of coronavirus most prone to mutation so single, effective vaccine may prove elusive** ? **Potential challenges with commercial scalability, including for Moderna, given lack of commercial experience**	? **Mutation of spike proteins may limit long-term effectiveness of antibody-based approach** ? **Potential of ACE2 inhibition?** ? **For antibodies IV administration may limit use to prophylaxis in institutionalized patients**	✓ **RNA polymerase not prone to mutation, so mechanism may avoid resistance** ✓ **Several drugs in active clinical trials** ? **Only effective before viral peak? Challenging for IV (e.g., remdesivir) but easier for orals (e.g., chloroquine)**	? **Potential to reduce mortality in the near term** × **Provides symptomatic benefit rather than disease modification**
Promising Therapies	• **mRNA:** Moderna, CureVac, BioNTech • **Recombinant Viral Protein:** Sanofi	• **Regeneron:** Past success with VelociSuite in Ebola • **Chloroquine:** Oral formulation may be effective if given prophylactically	• **Remdesivir (Gilead):** Broadly viewed as the most promising potential treatment • **Favipiravir (Toyama Chemical)**: Demonstrated improved viral clearance	• **IL-6s: Currently most attention is being paid to marketed IL-6s Kevzara (Sanofi/Regeneron) and Actemra (Roche)**
Timing	• **Moderna:** Immunogenicity data as early as June 2020 • **Commercial Scale Vaccine:** 18+ months	• **Regeneron:** Prophylactic antibody cocktail potentially by September • **Convalescent Antibodies:** Ongoing experimental use • **Other Antibodies:** 18+ months	• **Remdesivir:** Late-March/Early-April update on China trials • **Chloroquine:** Ongoing updates	• **Kevzara & Actemra:** May trial completion (commercial supply already in existence)

2 Overview of Potential Adoption Pathways for Novel Therapeutics

Given the severity of the pandemic, there is a competing tension between allowing for widespread adoption of therapeutics as quickly as possible and the need to effectively evaluate the efficacy of therapeutics to ensure the best long-term outcomes for individual patients and society. Adoption in the community is likely to evolve in parallel to official trial frameworks, which will need to be effectively coordinated by regulatory agencies to ensure validity

How Will Adoption Unfold

Experimental Use Within Individual Centers

- **Experimentation with drugs approved for other indications and through compassionate use pathways**
  - FDA moving to accelerate compassionate use pathways

Clinical Case Reports

- **Anecdotal evidence may drive broader adoption and trialing (off-label/compassionate use)**
  - Seen with uptick on chloroquine TRx following case reports coming out of China

Inclusion in Clinical Guidelines

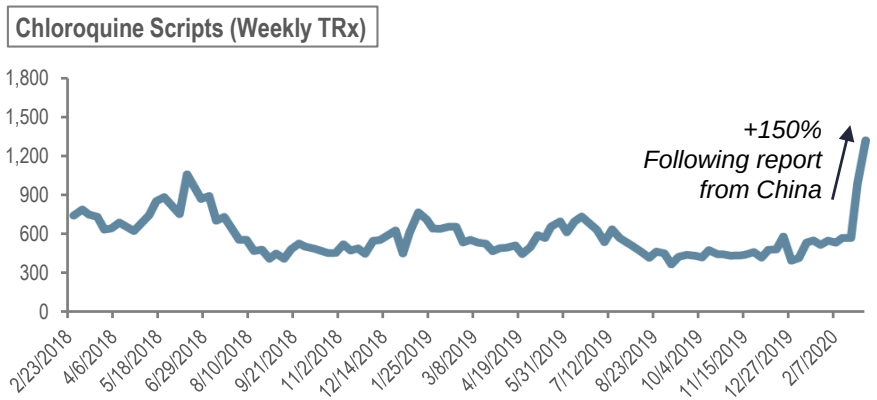
- **Guidelines based upon emerging evidence are already being published in China with the NHS and other agencies likely to follow suit**
  - Likely to drive broader community adoption

Clinical Trial Results/ Approval

- **Final adoption and market access will ultimately be driven by registrational data and regulatory agency approvals**

Chloroquine US TRx

- **Prescription data (as of March 6) showed chloroquine TRx continued to spike, suggesting there is real-world demand**
  - Script spike by ~150% (+760 scripts in week ending March 6 vs. week ending February 21 (i.e., spiking following chloroquine clinical report from China on February 21)
- **Use outside of trials may complicate value of data and ability to conduct randomized trials going forward**
- **Compassionate use allowances could drive further off-trial uptake if continued benefit is observed in a real-world setting**



Source: Baden et al. NEJM. October 2017; Gottlieb & McClellan. Duke. March 2020.

2 Challenges of Conducting Trials in a Pandemic

The challenges of conducting clinical trials during pandemics potentially undermine the quality of data generated and also put additional people at risk of transmission; a coordinated effort led by a centralized task force in the U.S. and globally will be critical to ensure the ethicality, quality and safety of trials

	Challenges	Policy Proposals[1]
Ethical Considerations	• **Given level of lethality and risk of transmission, there are ethical considerations for conducting a placebo-controlled trial[2]** – Given novelty of disease, historical controls are not well documented and not adequate alternatives – Complications from evolving use of supportive care measures	• **Task force empowered to act quickly and coordinate with manufacturers federal partners could be necessary to ensure quality** • **Placebo-controlled trials continue to be the gold-standard for identifying efficacy but will need to be well-coordinated to ensure comparability** – Efficient trial framework with novel approaches to data collection outside the standard trial site paradigm, given need for isolation – Master protocols that allow for evaluation of multiple drugs within the same trial – Potential use of cluster-randomized design to assess a prophylactic treatments • **Use of expanded access with ongoing monitoring can be used to provide potential benefit to a larger patient population without undermining trials and gathering useful information**
Multiple Uncoordinated Trials of Inconsistent Quality	• **Multiple trials for the same asset are being sponsored by companies, investigators and governmental agencies (in particular, assets already approved for other indications), confounding results and comparability across trials** – Trial design and protocol varies significantly, creating more confusion than clarity	
Increased Risk of Transmission Through Trials	• **Traditional trial design can increase risk of transmission** – For prophylactics and vaccines, traditional physical trial site design may put participants and providers at greater risk of infection	

Source: Baden et al. NEJM. October 2017;

1 Gottlieb & McClellan. Duke. March 2020.

2 Trial in which a subset of patients don't receive active treatment and establish a control group for comparison isolate the benefit attributable to the drug candidate (considered the gold standard).

2 WHO Global Trial

On March 18th, the World Health Organization announced plans for a coordinated multiarm, multicountry trial of four promising coronavirus therapies that addresses some of the challenges of conducting clinical trials during a pandemic; increasing coordination among a consortium of pharma manufacturers also has potential to help

Overview

- **The WHO announced plans for the SOLIDARITY Trial on March 18th**
  - Randomized
  - Multiarm trial of four drugs/drug combinations
  - 10 countries participating to date: Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland and Thailand
- **Similar trial had been launched by WHO for Ebola in November 2018 with results in August 2019**
  - Size of coronavirus outbreak could lead to significantly faster results for SOLIDARITY with potential for a readout in a few months

Drug / Drug Combinations Being Tested

1. **Chloroquine**
2. **Lopinavir—ritonavir**
3. **Lopinavir—ritonavir with interferon beta**
4. **Remdesivir**

Quotes

"The mere fact the WHO is sponsoring the trial suggests that efforts in China to test these drugs may not have come up with enough data to indicate whether any were of use to prevent patients from developing severe disease or save those with severe disease from death."

STAT NEWS, MARCH 18, 2020

"Multiple small trials with different methodologies may not give us the clear strong evidence we need about which treatments help to save lives"

WHO DIRECTOR-GENERAL TEDROS ADHANOM GHEBREYESUS, MARCH 18, 2020

"The good thing about the trial is… that the randomization could be adjusted to the drugs available in each individual hospital over time [and] we can include additional arms or drop arms as our global data safety and monitoring committee advises we should do."

WHO R&D HEAD ANA MARIA HENAO-RESTREPO, MARCH 18, 2020

2 Overview of the Evidence for Chloroquine Efficacy

Recent data out of France for chloroquine has raised hopes of efficacy—in particular in combination with another anti-infective used to help manage pneumonia. On March 30, the FDA issued an EUA for (hydroxy)chloroquine despite the lack of any pivotal data on the drugs' efficacy and safety

Overview

Key Details

- **Mechanism:** Increases endosomal pH, resulting in impaired virus/cell fusion
- **Administration:** IV or oral
- **Approval Date / Indications:** 1947 / antimalarial, proposed as an antiviral in mid-2000s
- **Rationale / Past Evidence:** Success in early trials in China and France

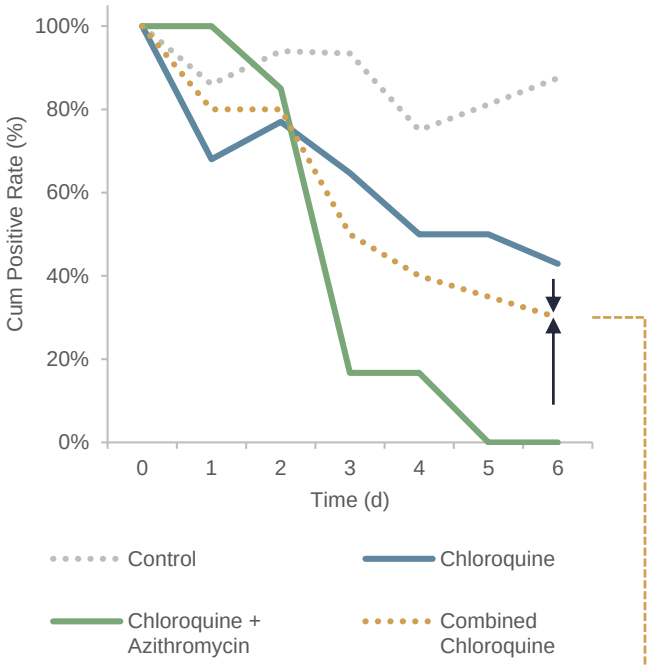
Recent Data[1]

- **In trial run by the Méditerranée Infection Foundation in Marseille, hydroxychloroquine was shown to dramatically reduce viral load in 26 COVID-19 patients versus a control group of 16 COVID-19 patients not on the drug**
  - Hydroxychloroquine and chloroquine are structurally similar and widely used as anti-malarials; hydroxychloroquine was developed to have fewer drug-drug interactions
- **Activity was enhanced when used in combination with azithromycin**
  - While azithromycin is an antibiotic, it has shown activity in viral infections and also has anti-inflammatory benefits
- **Chloroquine reduced viral positivity rate to 43% after six days of treatment compared to 90% positivity in the control group**
  - 0% in chloroquine + azithromycin arm
- **A subsequent IHU study showed a similar effect in a larger sample size but with similar trial design issues (e.g., no control)**
- **In a separate, randomized trial in mild COVID-19 patients didn't show major benefit though small sample (N = 30 with 1:1 randomization) and there was directional benefit on rate of viral clearance and CT scans albeit modest[2]**
  - Lower dose than many other (hydroxy)chloroquine studies (no loading dose and 400mg QD vs loading doses and BID dosing in many other trials and 600mg QD in IHU study)
  - Use of antiretrovirals in the control further confound results
- **A third randomized study (N=62) conducted in the Wuhan region showed encouraging results with statistically significant improvements on various clinical endpoints including duration of cough and fever and improvement in pneumonia. The results are promising especially considering no loading dose was administered; however, no details were provided on background antiviral therapies (allowed in treatment protocol) or comorbidities across two arms both of which may have influenced the results**

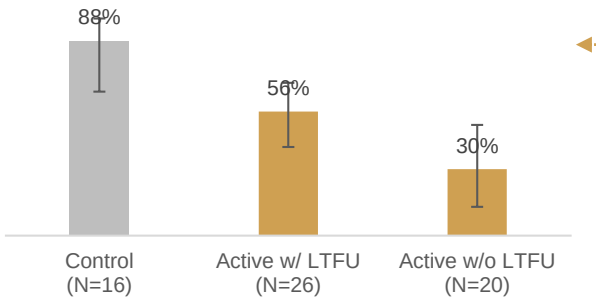
Key Questions

- **Control was not randomized (gold standard). All patients were offered therapy with patients who refused serving as the control, which creates possible selection bias**
  - Healthier patients forgoing treatment would suggest even better benefit with drug
  - Conversely sicker patients on existing medications with a known drug-drug interaction or a contraindicated comorbidity forgoing treatment (included in control) would suggest the control could be more in line with active arms
- **Six patients were "lost to follow up" (LTFU), implying they had poor outcomes (Three worsened and were transferred to the ICU and one died). Imputing these data reduces the observed benefit (though still better than control—see chart at right)**

Chloroquine +/- Azithromycin



Patients Testing Negative at Day 6



Source: Equity research.

1 Gautret et al. IHU Mareseille.

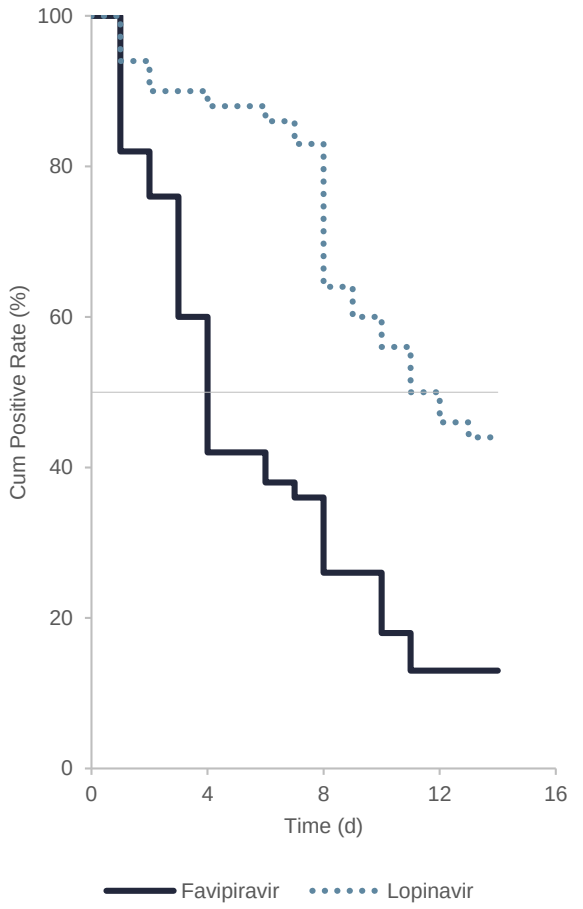
2 Chen et al. Shanghai Public Health Clinical Center. March 2020.

2 Overview of Recent Developments – *Favipiravir*

Recent data from China has also shown benefit—both clinical and in terms of viral clearance—and has reinforced optimism for remdesivir given the positive readthrough based on preclinical data

Overview	
Key Details	• **Mechanism:** Inhibit the RNA dependent RNA polymerase (RdRp) of RNA viruses • **Administration:** Oral • **Approval Date / Indications:** 2014 / influenza and Ebola • **Rationale / Past Evidence:** Test dosages appeared effective in mild cases in Japan
Recent Data[1]	• **236-patient, non-randomized (though two time-based cohorts for favipiravir and lopinavir), open-label trial of moderate patients (>93% oxygen saturation)** – Enrollment limited to patients <7 days from disease onset • **Shortened time to viral clearance materially: 4 days vs 11 days for lopinavir** • **91% of pts on favipiravir had chest CT scan improvement vs 62% on lopinavir**
Key Questions	• **While successful at treating mild and asymptomatic patients, in a study of 70-80 patients in Japan, Favipiravir was not shown to be as successful in treating patients where the virus had already multiplied**

Favipiravir vs Lopinavir Viral Clearance



Source: Equity research.
1 Cai et al. Engineering. March 2020.

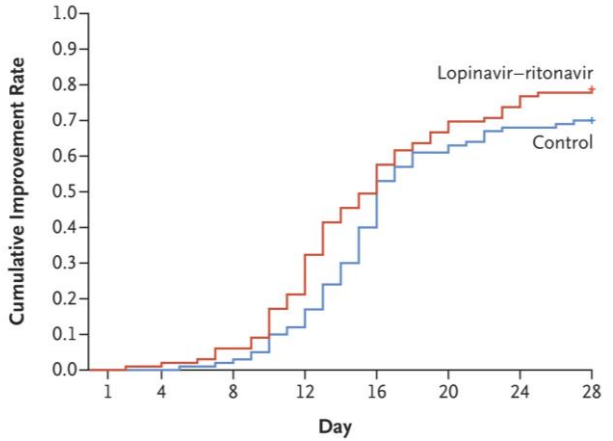
2 Overview of Recent Developments – *Lopinavir–Ritonavir*

A well-designed trial of the combination of lopinavir–ritonavir unfortunately failed to demonstrate a clinical benefit relative to the control. While there was a numeric (i.e., non-statistical significant) benefit in mortality for a subset of patients treated earlier in the course of the disease, the results were inconclusive

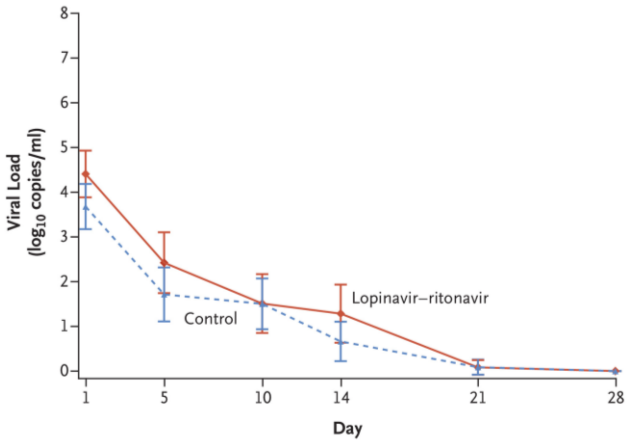
Overview

Key Details	• **Mechanism:** Protease inhibitor • **Administration:** Oral • **Approval Date / Indications:** 2000 / antiviral, HIV • **Rationale / Past Evidence:** Previously used to treat SARS
Recent Data[1]	• **Results of 199 patient, randomized, controlled, open-label trial of hospitalized adult patients with confirmed SARS-CoV-2 infection** • **Primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital** • **Numeric but not statistically significant benefit in time to clinical improvement and mortality shown** – 13.8% discontinuations due to AEs – Reduced mortality (19.0% vs. 27.1%) was observed in a post hoc subgroup analysis of those treated within 12 days after the onset of symptoms – No reduction in viral load demonstrated
Key Questions	• **Is benefit shown in patients treated earlier a true signal or just a statistical anomaly?**

Times to Clinical Improvement



Mean Change from Baseline in Viral Load



Source: Equity research.
1 Cao et al. NEJM. March 2020.

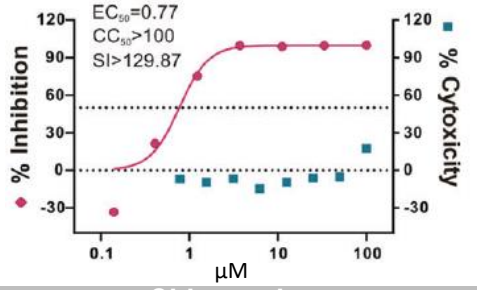
2 Overview of Recent Developments – *Remdesivir*

Remdesivir has been viewed by many as the most promising anti-viral in development based on its mechanism and preclinical data suggesting better potency than other drugs in development; however, IV administration may limit benefit to hospitalized patients

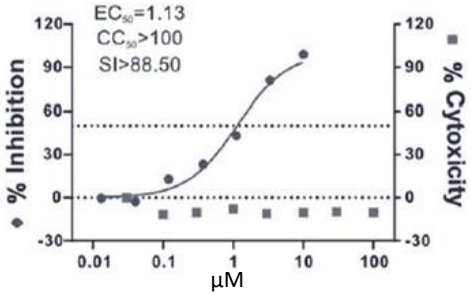
	Overview
Key Details	• **Mechanism:** Nucleotide inhibitor • **Administration:** IV • **Approval Date / Indications:** Ph. III / Ebola • **Rationale / Past Evidence:** Active against many ssRNA viruses (i.e., SARS, MERS)
Recent News	• **Originally developed for Ebola, effective against numerous single-strand RNA viruses, including the corona viruses SARS and MERS** • **Five clinical trials underway:** – NIH has an adaptive-design Ph. II trial that has already started in Nebraska – Two Ph. III trials underway at China-Japan Friendship Hospital in Hubei, double-blinded and placebo-controlled • Preliminary data expected as early as April – Gilead is starting two open-label trials, one with no control arm and one with an (unblinded) standard-of-care comparison arm, which are likely read-out first • **WHO's R&D Blueprint Clinical Trials expert group named the nucleotide analog the most promising candidate for COVID-19 in a Jan. 29 draft report**
Key Questions	• **EC50 is an in vitro measure of potency (itself is a function of a drug's affinity and efficacy), and remdesivir has performed better than other drugs in development on this measure (e.g., chloroquine, favipiravir), raising question on readthrough from early clinical trials in those assets:** – E.g., if favipiravir performs well, shouldn't remdesivir do even better? • **Inclusion criteria for time since illness onset (≤12 days) in the severe cohort may be too late to show a benefit, as viral peak may have occurred** • **Ceased fulfilling compassionate use requests due to volume while trials are completed**

EC50[1]

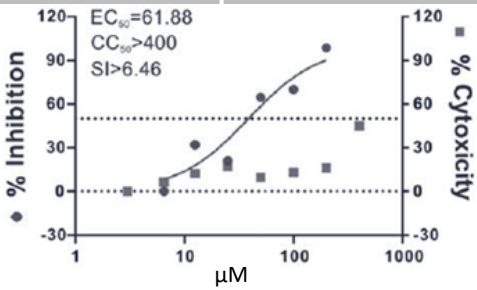
Remdesivir



Chloroquine



Favipiravir

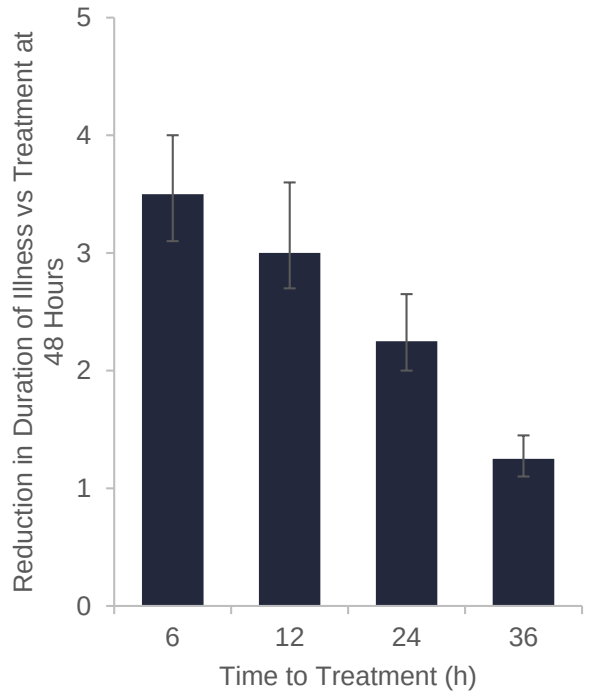


Source: Equity research.

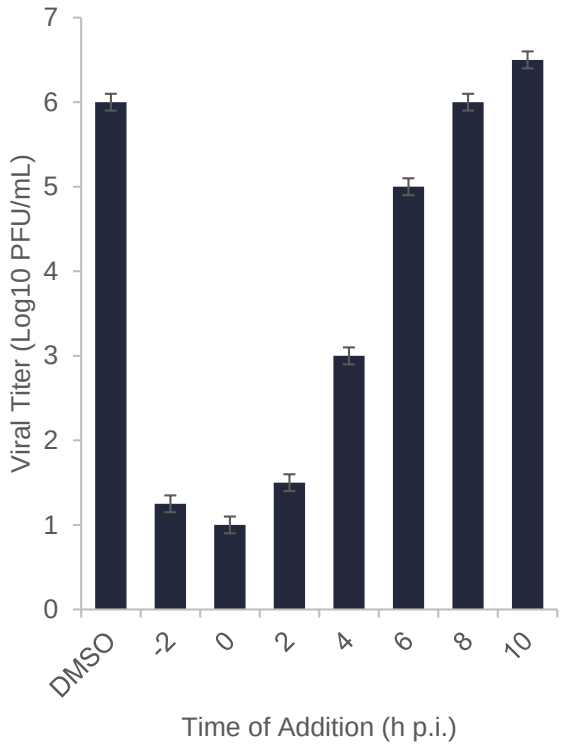
2 Antivirals May Show Greater Efficacy if Initiated Earlier

While early treatment may provide the greatest benefit, a median of 5 days for onset for symptoms[1] and viral peak at 7+ days could leave a limited effective treatment window. Given remdesivir is an IV infusion, there may also be logistical barriers to prompt treatment

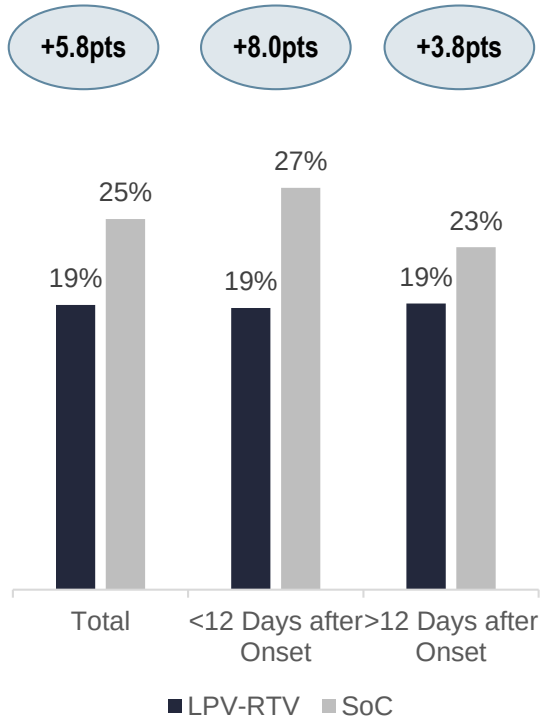
Tamiflu Benefit Decreases with Delayed Treatment



Mouse Models Suggests Remdesivir Efficacy Improves When Initiated Earlier



Lopinavir–Ritonavir Showed a Slight Mortality Benefit in When Initiated Earlier[2]



1 Lauer et al. Annals of Internal Medicine. March 2020.
2 Cao et al. NEJM. March 2020.

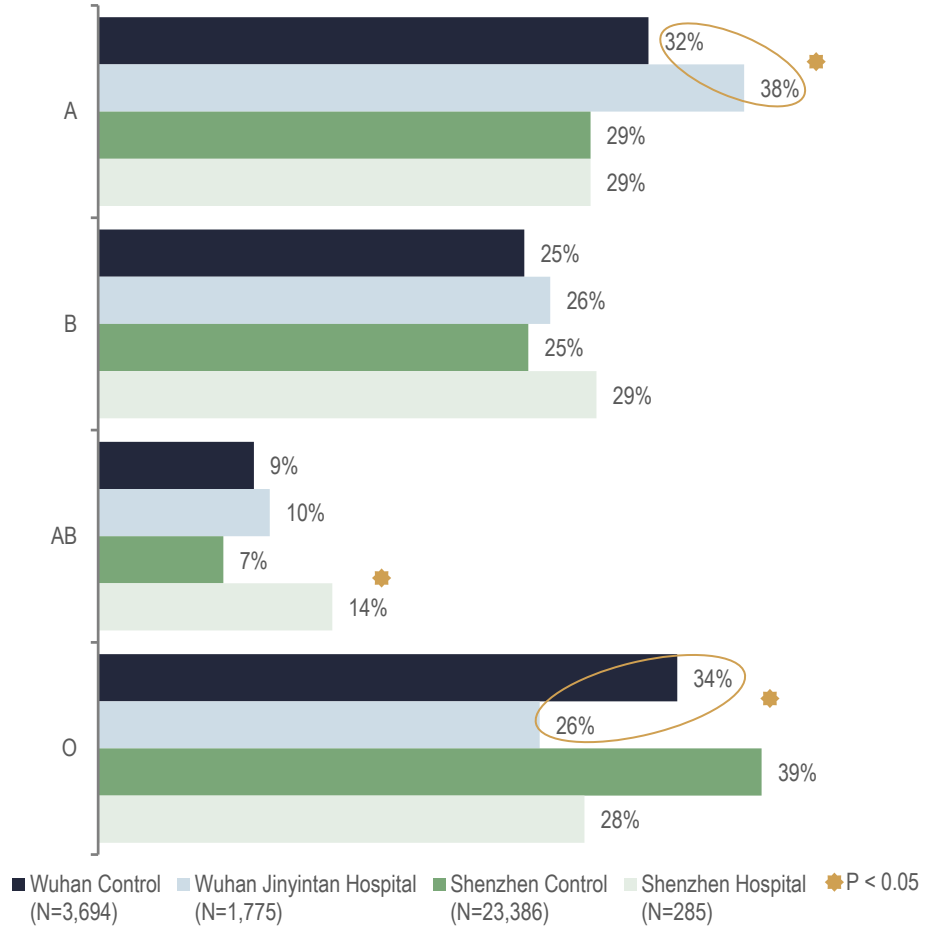
2 Susceptibility by Blood Type May Point to Other Strategies for Treatment

An evolving understanding of coronavirus is opening potential new pathways to explore for treatments while improving perspectives on transmission scenarios

Overview

- **A preprint of a study to be published in medRxiv in March, demonstrated a higher incidence of infection among patients with blood type A and a lower incidence among those with blood type O**
  - Study also pointed to a benefit in outcomes for type O patients versus type A
- **Relationship between ABO type and susceptibility to infection is well-covered in scientific literature (including malaria)**
  - Phenomenon also observed with 2003 SARS outbreak (another coronavirus)
  - Work had been done to elucidate the mechanism and implications for transmission patterns—demonstrated anti-A/B antibodies (which are expressed in O type patients) prevent cellular uptake of the virus by inhibiting viral bindings to ACE2
- **Ultimately, study design does not allow for definite understanding:**
  - Observational, case-control study to identify a supposed causation vs prospective, randomized trial (not all variables are controlled with the assumption that they are equally distributed except for the one under question)
  - No control for clinical/morbidity benefit vs prospective, randomized trial
  - Various statistical anomalies and lack of clarity on controls for biases
- **Effect could point to therapeutic mechanisms to explore (e.g., other pathways for preventing ACE2 binding like camostat mesylate)**
- **Effect may also relate to other patterns of susceptibility that have been observed: for example, anti-A/B antibodies peak at ages 5-10 then decline as people age, and therefore, may contribute to the mild presentation and low susceptibility of children**

Infection Distributions by Blood Type vs Normal Controls



Source: Zhao et al. MedRxiv. March 2020; Guillon et al. Glycobiology. September 2008.

2 Vaccines: Five Key Questions as Trials Begin

While vaccines potentially represent the long-term solution to combating coronavirus, there are a number of key questions that need to be answered, and no commercially viable vaccines are expected to be available for 18+ months

Commentary

- **Vaccines induce adaptive immunity by introducing a coronavirus viral antigen (i.e., spike protein) either through a protein, mRNA (which produces the protein) or attenuated virus**
- **A number of vaccines are currently in development: however, they are not expected to be widely available for 18+ months**
  - A number of novel vaccines are also in development, including PittCoVacc, a patch vaccine that utilizes a microneedle array to increase potency
- **Significant unknowns surrounding SARS-CoV-2: Specifically, do people develop immunity, and if they do, how long it lasts?**
  - Studies of other coronaviruses have shown acquired immunity in humans, but it is short lived
  - MERS and SARS have shown equivocal results:
    - MERS, after infection, antibodies drop significantly
    - SARS antibodies remain in the body for up to 15 years, but it is unclear whether this immune response is enough to prevent reinfection
  - Study on two rhesus macaques showed they were not re-infected when exposed to SARS-CoV-2 after infection
- **Many SARS-CoV-2 vaccines in development are designed to train the immune system to make antibodies that recognize and block the spike protein that the virus uses to enter human cells**
  - However, that might not be the full solution; blocking other viral proteins or creating T-cells that kill infected cells may be necessary
- **Numerous concurrent animal trials and Ph. I human trials are in progress; however, as vaccines are given to large numbers of healthy people, there is a higher bar for safety than drugs given to people who are already ill**

Key Questions

1. **Do people develop immunity?**
2. **If humans do develop immunity, how long does it last?**
3. **What kind of immune response should vaccine developers look for?**
4. **How do we know if a vaccine is likely to work?**
5. **Will it be safe?**

2 Timeline of Key Milestones

Vaccines are not expected to be widely available for 18+ months, but various antivirals are currently being tested in China and the U.S. that could have an accelerated path to market over the next several months

	Drug	Milestone	Controlled?	2020 Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec	2021 1H	2H
Vaccine	mRNA-1273	Ph 1: First Patients Dosed	✗											
		Ph 1: Low-Dose Immunogenicity Data	✗											
		Ph 1: Primary Completion[1]	✗											
	INO-4800	Ph 1: Initiation	✗											
	BNT162	Ph 1: Initiation	✗											
	PittCoVacc	Ph 1: Initiation	✗											
	Novavax/Emergent	Ph 1: Initiation	✗											
	Generex Biotech	Ph 1: Initiation	✗											
	Vaxart/Emergent	Ph 1: Initiation	✗											
	CureVac	Ph 1: Initiation	✗											
	Altimmune	Ph 1: Initiation	✗											
	J&J/BARDA	Ph 1: Initiation	✗											
		Ph 1: Primary Completion	✗											
	Takis Biotech	Ph 1: Initiation	✗											
	Sanofi	Ph 1: Initiation	✗	?										
Prophy-lactic	REGN-EB3	Ph 1: Initiation	✗											
	Lilly/AbCellera	Ph 1: Initiation	✗											
	Medicago	Ph 1: Initiation	✗											
Antiviral	Remdesivir	Ph 3: China Trial Interim Results	✓											
		Ph 3: U.S. Trial Data	✓											
	Favipiravir	Various Ongoing	✓											
	Kaletra/Aluvia	Various Ongoing	✓											
	Chloroquine	Ph 4: China Trial Efficacy Results	✓											
Immune Mod.	Actemra	Expected China Trial Completion	✓											
	Kevzara	Expected U.S. Trial Completion	✓											

Source: Company filings, equity research.

1 On March 20th, Stephane Bancel, the CEO of Moderna, indicated that while a commercially-available vaccine is not likely to be available for at least 12-18 months, it is possible that under emergency use, a vaccine could be available to some people, possibly including healthcare professionals, in the fall of 2020.

2 Other Considerations

Beyond clinical discovery and development of novel and repurposed therapeutics, there are a number of additional factors that will ultimately govern effective use and widespread adoption

Regulatory Review

- **If early trials show benefit, placebo-controlled clinical trials may not be viewed as ethical and instead open-label studies will be conducted**
- **Proposed CDER task force with defined clinical trial framework and master protocols (similar to WHO SOLIDARITY study) will potentially expedite review and identify the most effective therapeutic regimens**

Commercial Scale-up

- **Small molecule antivirals (including some that are already commercialized) would be the most readily saleable with Gilead currently making investments in commercial-scale manufacturing for remdesivir**
- **H1N1 outbreak in 2009 was biphasic and new vaccine benefited from capacity in flu vaccine manufacturing facilities that had finished flu batches**
- **Moderna has communicated the ability to produce 10m batches by fall**

Market Access

- **Reimbursement by government payors likely to be quickest through FDA approval for COVID-19 with potential for commercial payors to add products approved in other indications (e.g., chloroquine, Actemra) to formularies based on guidelines (government or compendia) prior to explicit approval for COVID-19**
- **Compassionate use pathways will allow for interim use and reimbursement of investigational treatments**

3 Objectives of Diagnostic Testing by Transmission Stage and Type of Test

The objective of diagnostic testing varies at different stages of a pandemic, evolving from a tool for containment (e.g., rapidly identifying infected individuals to drive contact tracing) to a tool for surveillance. As the pandemic progresses, diagnostics and serological antibody testing begin to play a more important role in informing mitigation policy and eventually become a surveillance tool

Containment	Mitigation	Surveillance
• **Rapid, widespread testing (as in S. Korea) is critical for early-stage of pandemic** – Facilitates contact tracing and allows for isolation of contagious individuals • **CDC should rapidly develop and validate protocols with clear EUA guidelines to facilitate scaling national and local laboratory capacity** – Game-changing launch of Abbott's rapid, point-of-care SARS-CoV-2 test for its ID NOW system, originally developed to test for Strep and the flu in POC settings, which has the largest installed base of any molecular POC testing platform in the U.S.	• **With widespread transmission, monitoring infection rates is critical for informing policy decisions (e.g., when to end shelter-at-home orders)** – Testing a representative sample of the population for serological antibodies can inform level of acquired immunity in the population (success shown in limited applications in Italy) • **Drive-thru, point-of-care and at-home testing become important tools for monitoring rate of infection while avoiding transmission at outpatient testing sites**	• **Much like initial stage of the pandemic, rapid testing and contact tracing critical for avoiding resurgence** – Point-of-care diagnostics at the level of PCPs become important tool for quickly identifying and isolating infections in the community • **Periodic serological antibody testing critical for monitoring population-level immunity (quality and duration)** – Particularly important given weak/short-lived immunity observed with SARS and MERS

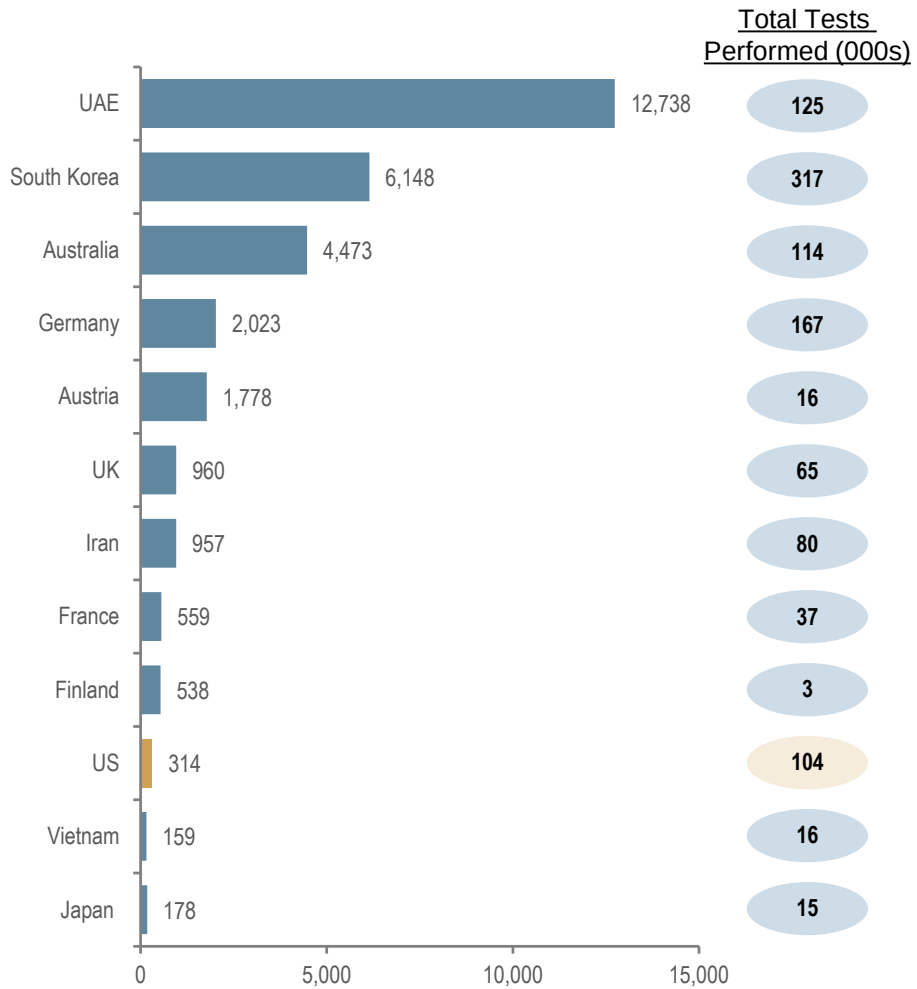
Key Learnings for Pandemic Preparedness

- **CDC must be prepared to quickly scale diagnostic capabilities with clear guidelines for EUA**
  - Supply chain issues should be addressed early (e.g., swabs, reagents)
  - Testing criteria should be relatively inclusive
- **Contact tracing can be augmented through digital / AI tools that can help with early containment**
- **Avoiding transmission by separating testing from hospitals where infected individuals are treated and reducing contact between providers and patients is critical**
- **Developing antibody testing is as critical as infection diagnostics and should be rapidly developed / deployed**

3 Current State of Coronavirus Testing

For effective use of antivirals, widespread and fast diagnostics (including point-of-care and at-home tests) will be necessary to identify infected patients soon after exposure to interrupt viral replication prior to peak, but the U.S. has struggled with testing capacity and speed

Number of Tests Performed Per Million People[1]



Commentary

- **In a pandemic, it is key to be able to test all suspected cases, but due to testing shortages/quality issues that began at the start of the U.S. outbreak, only patients with more severe symptoms have been able to get tested**
  - When COVID-19 appeared in the U.S., the CDC developed its own test, which, due to issues with false positives, was only allowed to be administered in a few state labs
- **On February 29, the FDA issued emergency use authorization (EUA) guidance for companies developing SARS-CoV-2 testing at the behest of the CDC**
- **However, labs currently developing their own assays for COVID-19 virus detection face reagent supply shortages**
- **As of April 3, only 25 manufacturers have been approved to test for SARS-CoV-2 via the EUA guidelines**
- **Beyond issues with test volume, the act of going to a testing site may expose individuals to SARS-CoV-2 by placing them in large groups of sick individuals**
- **To gain real insight into how the pandemic is progressing, it is necessary to understand how the percentage of positive cases—not the number—changes day by day**
  - This would require extensive "smart testing" which even South Korea, the nation seen as perhaps the most successful at testing its population, has been unable to manage

LAZARD *Source: CDC, FDA, Our World in Data, STAT News, The Economist and covidtracking.com.*

1 Latest figures as of March 20, 2020.

3 Key Considerations Surrounding Coronavirus Testing

Accuracy	• **Following updates to CDC test protocols, accuracy of PCR testing done by certified labs assumed to be high** • **However, specimen type and method of collection can create a disparity in results:** – Recent study of specimens tested by rRT-PCR showed significant differences in positive rates across the same patients: bronchoalveolar lavage fluid (14 of 15; 93%), sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%) – Given potential for transmission through aerosolized fluid/sputum, contagious individuals tested by nasal swab (most common method) may be falsely given negative test result • **Home tests also raise concerns that specimens may not be correctly collected (e.g., deep enough swap) also creating potential for contagious individuals to be incorrectly diagnosed and not take necessary steps to avoid infecting others** – False negative risk must be weighed against risk of contagious individuals infecting others while seeking outpatient test)
Regulatory	• **Initial lack of clarity under updated Emergency Use Authorization guidance led to launches of various home test kits (Everlywell, Nurx, Carbon Health) that collected sample by post and tested in CLIA certified labs** – FDA subsequently clarified that home testing was not covered by EUA and testing has been halted • **Scanwell Health is pursuing EUA for at-home serological test with expected availability in early summer**
Latency	• **Standard lab testing on average is taking several days leading to uncertainty for patients / providers on self-isolation and care** • **Various labs/companies (e.g., Cleveland Clinic, Heat Biologics) are working to reduce testing time to a matter of minutes/hours, which will have significant implications for more informed guidance on self-isolation and treatment** – Abbott received EUA for 5-minute point-of-care test
Risk of Infection from Outpatient Testing	• **Drive-through testing have become a common method (both public and private e.g., CVS, Walgreens) to avoid transmission between individuals at outpatients testing sites** – However, transmission is highest in dense urban areas which are less conducive to drive-in testing sites – Home testing would be ideal solution assuming accuracy and latency can be adequately addressed
Serological Testing	• **Development of testing for serological antibodies will be important for informing perspectives on duration and quality of immunity** • **Surveillance of patterns in immunity will be key for policy responses** – Small scale efforts Vo, Italy resulted in 90% reduction in transmission and larger-scale initiatives are underway in the UK

3 Key Recent Developments in Coronavirus Testing

	Company	Date	Capacity	Test	Rate
Diagnostic Players & Large Labs	Roche	3/12/20	900k / week	Cobas	96 results 3hrs
	ThermoFisher Scientific	3/13/20	5m / week	TaqPath Combo Kit	94 results 4hrs
	Hologic	3/16/20	600k / month	Panther Fusion	3hrs
	LabCorp	3/16/20	20k / day		
	Quidel	3/17/20		Lyra Assay	
	Quest Diagnostics	3/17/20	20k / day		
	Abbott	3/18/20	1m / week	RealTime	
	DiaSorin Molecular	3/19/20		Simplexa Direct Assay	1hr
	GenMark Dx	3/19/20	100k / month	ePlex RUO Test Kits	2hrs
	Primer Design[1]	3/20/20		Genesig PCR assay	
	BioFire[2]	3/23/20		RP2 Panel	
	PerkinElmer	3/24/20		Nucleic Acid Detection Kit	1hr
	Avellino	3/25/20	200k / month	AvellinoCoV2	4hrs
	BGI Global Genomic Services	3/26/20	300k / day	RT-PCR	
	Luminex	3/27/20	300k / month	NxTAG	96 results 4hrs
	NeuMoDx	3/30/20		NeuMoDx Assay	288 results hr 20min
	QIAGEN	3/30/20	6.5m / month	QIAstat-Dx Test Kit	1hr
	Ipsum Diagnostics	4/1/20		COV-19 IDx	
	ScienCell Research Laboratories	4/3/20		RT-qPCR Detection Kit	
	Co-Diagnostics Inc.	4/3/20		Logix Smart Test	
	Ortho Clinical Diagnostics	4/6/20		VITROS Reagent Pack	150 results 1hr

Commentary

- **Tests developed by diagnostics players must be run on their own systems (i.e., Roche & Abbott)**
- **A number of available tests can only be performed at CLIA labs certified to perform high complexity tests**
- **Turn around time of 3-4 days for specimens that must be sent out to a lab (i.e., LabCorp, Quest) to be processed**
  - Reagents are creating bottle-necks at many labs
- **Smaller diagnostics players are producing kits that can be run in smaller hospital labs, reducing turnaround time (i.e., Ortho Clinical Diagnostics)**
- **Diagnostic players are ramping up manufacturing, with many employing emergency task forces to increase production**

Source: FDA, FierceBiotech, ScienceMag, STAT News and industry publications.

1 Subsidiary of Novacyt.

2 Subsidiary of bioMerieux, which launched three diagnostic tests for SARS-COV-2 in early March.

3 Key Recent Developments in Coronavirus Testing

	Company	Date	Capacity	Test	Rate	Commentary
Point-of-Care & At-Home	Cepheid	3/20/20	5k in U.S.	GeneXpert System	45min	• Speed of POC testing reduces the potential of a contagious individual infecting others while waiting for results • Helps alleviate shortages in the U.S. • Abbott launched a test on its ID NOW system, the most widely installed molecular diagnostic tool in point-of-care settings • Provides positive results in 5 minutes and negative results in 13 minutes • Abbott's ID NOW system was originally developed to test for Strep and the flu in POC settings • Abbott's platform's speed and accessibility makes it a game-changer in SARS-CoV-2 testing
	mesabiotech	3/23/20		Accula Hand-Held	30min	
	Abbott	3/27/20	50k / day	ID NOW (Point-of-Care)	5-13min	
	NURX, LetsGet Checked, Carbon Health, everlywell	• FDA issued a warning that all at-home tests are unauthorized • Home tests could be beneficial in preventing the spread of the disease, however, the risk of false negatives may outweigh that positive as individuals spread the disease while thinking they are virus-free				
Serological	SD BIOSENSOR / HENRY SCHEIN	3/26/20		Standard Q IgM/IgG Rapid POC Test	15min	• Only Cellex's and BD's test are approved by the FDA as of April 3, 2020, Cellex's must be done in a lab while BD's is point-of-care • Testing a person's blood for SARS-CoV-2 antibodies can determine not only if they have an active infection, but if they had an infection in the past and may not have realized it • Large-scale data from such tests—e.g., showing what fraction of people in Wuhan, China, might now be immune—is still lacking or at least not public
	BODYSPHERE	3/31/20		BodySphere's Rapid Test[1]	2min	
	Cellex™	4/1/20		qSARS-CoV-2 IgG/IgM Rapid Test	15-20min	
	BD	4/2/20	1m+	BioGx for BD MAX[2]	15min	
	QUOTIENT	4/6/20		MosaiQ MicroAssay	3000/day	

Source: FDA, FierceBiotech, ScienceMag, STAT News and industry publications.

1 91% clinical sensitivity rate and a 99% specificity rate.

2 89% clinical sensitivity rate and a 91% specificity rate.

Appendix: Details on Therapeutics in Development for COVID-19

4 Vaccines in Development for COVID-19

Vaccine

Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
moderna	mRNA-1273	Ph. I	NA	mRNA-based vaccine with LNP vector	IM	Jun-2021	Stabilized form of SARS-CoV-2 spike (S); announced first patient dosed in Ph. I study on March 16; expects safety data by Spring and expects Ph. II post-safety data / Ph. III trial by Summer / early Fall. Potential that a vaccine for healthcare workers could be used under emergency use in Fall 2020
inovio	INO-4800	Ph. I	NA	SARS-CoV-2 immunoglobulin stimulant	IM	NA	Received FDA clearance to be tested in 40 volunteers, dosing to begin April 6th. $5mm grant from Gates Foundation to accelerate testing of intradermal delivery for INO-4800. Additionally, DoD awarded Ology Bioservices a ~$12mm contract to work with Inovio on DNA vaccines
CanSinoBIO	Ad5-nCoV	Phase I (China)	NA	Genetically engineered SARS-CoV-2 vaccine with AAV vector	IM	NA	Received Chinese regulatory approval in mid-March to start human trials of a vaccine against the COVID-19, tests will continue through YE2020
Pfizer[1] / BIONTECH	BNT162	Preclinical	NA	mRNA-based vaccine with LNP vector	IM	NA	Collaboration around BioNTech's mRNA vaccine, BNT162, which is expected to enter clinical testing by end of April 2020
NOVAVAX	Several	Preclinical	NA	Recombinant nanoparticle vaccine generating S protein antigens	IM	NA	Phase I trial to start by late spring 2020; received $4mm grant from CEPI to accelerate development
三叶草生物制药 Clover Biopharmaceuticals	COVID-19 S-Trimer	Preclinical	NA	Timerised fusion protein vaccine	IM	NA	Announced in February the identification of its vaccine candidate, which will enter pilot and preclinical testing
Johnson & Johnson	NA	Preclinical	NA	Nonreplicating viral vector; Ad26	-	NA	Announced the selection of a lead vaccine candidate and an expanded partnership with U.S. department of Health and Human Services to develop and manufacture more than one billion doses of a vaccine. Plans to initiate Phase 1 by September 2020, with the hope for emergency use authorization in early 2020
CODAGENIX INC.	NA	Preclinical	NA	Deoptimized live attenuated virus	IM	NA	Animal data in summer 2020. Co-developing vaccine with Serum Institute of India.
medicago	NA	Preclinical	NA	Plant-derived virus-like particle injected as vaccine	-	NA	Developed a virus like particle in March 2020, expects to initiate human trials of the vaccine by summer 2020
SANOFI	NA	Preclinical	NA	Protein subunit; S protein, baculovirus production	IM	NA	Initiate Phase 1 trial March 2021
INNOVATION PHARMACEUTICALS INC.	Brilacidin	Preclinical	Oral Mucositis, IBD, Acute Bacterial and Skin Infections	Defensin memetic; disrupts integrity of cell membrane; MOA in viruses still being elucidated	Oral	NA	Developing Brilacidin, a defensin-mimetic drug candidate, as a potential novel coronavirus (COVID-19) vaccine
LAIS	NA	Preclinical	NA	Genetic vaccine	IM	NA	As of March 17th, Takis' novel vaccine for COVID-19 was ready for preclinical development. If successful, human trials could begin in Fall 2020.

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
Note: Excludes academic studies and company research efforts with no specific drug candidates.
1 Pfizer is also investigating potential anti-viral candidates.

4 Vaccines in Development for COVID-19 (cont'd)

Vaccine

Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
StemRNA	NA	Preclinical	NA	mRNA based vaccine	NA	NA	Co-development with Shanghai East Hospital Tongji University; in the process of manufacturing vaccine samples with clinical trials planned to start in April 2020
UFOVAX	NA	Preclinical	NA	1c-SApNP vaccine platform	NA	NA	Spin-off company from Scripps research; UfoVax uses a proprietary one component self-assembling protein nanoparticle (1c-SApNP) vaccine platform technology. Being tested in animal models in the near future
GeoVax / BravoVax	NA	Preclinical	NA	Modified Vaccinia Ankara (MVA) Platform technology	-	NA	GeoVax announced on January 30th, it will use its MVA-VLP vaccine platform and expertise to design and construct a COVID-19 vaccine, with BravoVax providing further development and manufacturing support
VAXART	NA	Preclinical	NA	Non-replicating Viral Vector	Oral	NA	Developing an oral-recombinant COVID-19 vaccine. On March 19th, Vaxart announced a partnership with Emergent to manufacture the experimental oral candidate, Phase I to initiate in the second half of 2020
TONIX / SR Southern Research	TNX-1800	Preclinical	NA	Live modified horsepox vaccine	IM	NA	Tonix and Southern research announced on February 26th, the development of a vaccine for COVID-19 based on Tonix's proprietary horsepox vaccine
Greffex PROTECT AND HEAL	NA	Preclinical	NA	Adenovirus-based vector SARS-CoV-2 vaccine	-	NA	Greffex announced in mid-March it completed development of a COVID-19 vaccine and is ready to move on to animal testing
VAXIL VAXIL BIO THERAPEUTICS	NA	Preclinical	NA	-	-	NA	Developed a vaccine candidate based on signal peptide technology, utilizing Vaxil's proprietary VaxHit™ bioinformatics platform
科伦药业 KELUN PHARMACEUTICAL	NA	Preclinical	NA	Polypeptide targeting SARS-CoV-2 spike protein	-	NA	Sichuan Kelum announced February 2020 preclinical data in primates which showed good biological activity and safety; clinical trials are being planned
CSL Behring	NA	Preclinical	NA	Molecular clamp vaccine			In co-development with the University of Queensland; identified a vaccine candidate in February and are now beginning preclinical testing
British American Tobacco	NA	Preclinical	NA	-	-	NA	BAT's US bio-tech subsidiary, Kentucky BioProcessing (KBP), is developing a potential vaccine for COVID-19 and is now in pre-clinical testing. The company states that 1 and 3 million doses of the vaccine could be manufactured per week, beginning in June.
sorrento THERAPEUTICS / SmartPharm THERAPEUTICS	NA	Discovery	-	Monoclonal antibody SARS-CoV-2 vaccine	-	NA	The collaboration will utilize monoclonal antibodies against SARS-CoV-2 virus discovered and/or generated by Sorrento that will be encoded into a gene for delivery utilizing SmartPharm's non-viral nanoparticle platform
EXPRES²ION BIOTECHNOLOGIES	NA	Discovery	NA	-	-	NA	Developing vaccine which will utilize the company's Drosophila S2 insect cell expression system, and AdaptVac's Virus-Like Particle technology
Generex / EpiVax	NA	Discovery	NA	Ii-Key peptide	-	NA	Generex partnered with EpiVax in early February to use computational tools to predict epitopes to generate peptide vaccines against COVID-19. Generex will test the reactivity of these peptides in blood samples collected from recovered COVID-19 patients in China; phase I trial by late spring
iBio /	NA	Discovery	NA	-	-	NA	iBio and Beijing CC-Pharming, announced in early February, their collaboration to develop and test a new COVID-19 vaccine to be manufactured using iBio's FastPharming System

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
Note: Excludes academic studies and company research efforts with no specific drug candidates.

4 Vaccines in Development for COVID-19 (cont'd)

Vaccine

Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
Zydus Cadila	NA	Discovery	NA	DNA vaccine targeting S protein, live attenuated measles virus vectored	-	NA	Zydus Cadila was first to develop and indigenously manufacture vaccine for Swine Flu in 2010. Measles reverse genetics technology was first used to successfully develop the SARS-vaccine
Arcturus Therapeutics	NA	Discovery	NA	Self-transcribing and replicating RNA-based vaccine	IM	NA	Received grant from the Singapore Economic Development Board to develop a vaccine which could be effective at lower doses than other RNA therapeutics
Heat Biologics	NA	Discovery	NA	gp96 vaccine platform (heat shock protein activating T-cell response)	IM	NA	Launching program within Zolovax to develop a gp96-based vaccine against COVID-19
CureVac	NA	Discovery	NA	Synthetic mRNA SARS-CoV-2 vaccine	IM	NA	Expects to have a candidate ready for human testing by early summer 2020; increased its existing partnership with CEPI in January, including additional funding up to $8.3mm
altimmune	NA	Discovery	NA	Recombinant intranasal vaccine; activates humoral, mucosal and cellular immunity	Nasal	NA	Announced in February the application of the NasoVAX platform to developing a single does intra-nasal vaccine to begin clinical testing as early as August 2020
University of Georgia / EpiVax	NA	Discovery	NA	-	-	NA	EpiVax and the Ross lab at UGA are applying their rapid vaccine development process to the novel COVID-19 virus, the two companies previously partnered to develop a vaccine for the H7N9 Avian influenza
Bettapharma	NA	Discovery	NA	Dendritic cell vaccine	-	NA	Assessing universal dendritic cell vaccine for the potential prevention and treatment of COVID-19
Dyadic / IIBR	NA	Discovery	NA	-	-	NA	Using Dyadic's C1 gene expression platform to express gene sequences and targets developed by the Israel Institute for Biological Research into a SARS-CoV-2 vaccine
MVC	NA	Discovery	NA	SARS-CoV-2 vaccine	-	NA	As of February 2020, preclinical studies in animals were being planned in Taiwan
Sanofi / Translate Bio	NA	Discovery	NA	mRNA based SARS-CoV-2 vaccine	-	NA	Sanofi and Translate Bio will collaborate on the research and development of multiple candidates with the goal of advancing an efficacious and safe SARS-CoV-2 vaccine into clinical development in late 2020 or early 2021
HOTHTHERAPEUTICS	NA	Discovery	NA	SARS-CoV-2 vaccine platform	-	NA	HaloVax acquired an exclusive license to VaxCelerate from Massachusetts General Hospital in order to develop a vaccine to protect patients at risk of COVID-19 infection; the platform was developed to engage the patients immune system to identify and remove infectious agents
gsk / Innovax	S Trimer + Pandemic Adjuvant System	Discovery	NA	Trimer subunit vaccine + immune response booster	-	NA	Announced partnership Clover Biopharmaceuticals to evaluate a combination of GSK's pandemic adjuvant system with Clover's S-Trimer as a vaccine candidate. GSK also licensed an adjuvant system to Innovax to be applied to a vaccine it is developing with Xiamen University
	Skin Patch Vaccine	Discovery	NA	SARS-CoV-2 vaccine in skin patch form	Skin Patch	NA	Developed a vaccine delivered into the skin with a Band-Aid-like patch made of 400 tiny needles. When tested in mice, the vaccine produced antibodies to fight SARS-CoV-2 within two weeks
	NA	Discovery	NA	SARS-CoV-2 vaccine using a sendai virus vector	-	NA	ID Pharma and the University of Fudan partnered on a potential vaccine in February 2020; early research is being conducted

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
Note: Excludes academic studies and company research efforts with no specific drug candidates.

4 Prophylactics in Development for COVID-19

	Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
Repurposed	**Generic**	Chloroquine	Marketed	Malaria	Interferes with lysosomal activity and autophagy and disrupts membrane stability; MOA in viruses still being fully elucidated, however potent antiviral effect has been observed	Oral	NA	FDA authorized emergency use of chloroquine on March 30th. Demonstrated highly potent anti-viral effect; multiple companies have committed to manufacturing the drug. EC50=1.13 µM Recent trial from China (N=197, 500mg bid x 10d) showed that patients treated with chloroquine have a shortened time to reach undetectable viral RNA. The median number of days in the treatment group was three days compared to nine for the control group; additionally duration of fever was significantly shorter with treatment
	Generic	Hydroxychloroquine	Marketed	Malaria	Interferes with lysosomal activity and autophagy and disrupts membrane stability; MOA in viruses still being fully elucidated, however potent antiviral effect has been observed	Oral	NA	Several nationwide trials testing HCQ's benefit as both a prophylactic and a therapeutic are initiating in the U.S. in the next week (University of Minnesota (enrolling 3,000), Henry Ford Health System (3,000+) and NYU / University of Washington(2,000)) Recent trial at the Renmin Hospital at Wuhan University (n=62) showed significant improvements in fever, cough and pneumonia in a randomized, controlled trial of COVID-19 patients. Notably, no patients in the treated group progressed to severe illness vs 13% in the control group The FDA authorized emergency use of hydroxychloroquine on March 30th. Recent French trial of HCQ in combination with azithromycin (N=80) among non severe patients showed profound anti-viral effect; rapid fall of viral load (93% negative by day 8) and rapid hospital discharge (5 day mean length of stay). EC50=0.72µM.
	Generic	Foipan (camostat mesilate)	Marketed (Japan)	Chronic pancreatitis	TMPRSS2 inhibitor	Oral	NA	German researchers found in an in vitro study that camostat significantly reduces the infection of Calu-3 lung cells by SARS-CoV-2. To be investigated in clinical trials TBA
	CIDARA THERAPEUTICS	CD377	Preclinical	Influenza	Antiviral Fc conjugate	IV / IM / SC	NA	Developing antiviral Fc conjugates for coronavirus
Novel	sirnaomics	NA	Discovery	NA	RNAi	-	NA	Announced in January 2020 the development of RNAi Prophylactics and therapeutics for the treatment of COVID-19 patients suffering from Severe Acute Respiratory Infection

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
Note: Excludes academic studies and company research efforts with no specific drug candidates.

4 Anti-Viral Treatments In Development for COVID-19

Repurposed

Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
abbvie	Kaletra / Aluvia (Lopinavir / Ritonavir)	Marketed	HIV	Protease inhibitor	Oral	May-2020	Announced on March 23rd that the company would no longer enforce patent rights of Kaletra. Additionally, donated supply to Chinese health authorities for use as an experimental treatment; study primary completion date is May 30, 2020. No benefit beyond SOC was observed in recent trial of hospitalized adults with severe disease (results recently published in NEJM)
Roche / ascletis	Ganovo (Danoprevir)	Marketed	HepC	Hepatitis C NS3/4A protease inhibitor	Oral	Jul-2020	Small sample clinical trial of Ganovo and Ritonavir combination therapy on coronavirus; currently recruiting for Phase IV trial (n=125) with completion by July 31, 2020
FUJIFILM / HISUN 海正药业	Avigan (Favipiravir)	Marketed (Japan)	Influenza	RNA polymerase (RNAP) inhibitor	Oral / IV	NA	Approved as an influenza therapy; Hisun has been granted a clinical study to test its efficacy in the treatment of novel coronavirus pneumonia. Fujifilm markets Favipiravir for new strands of influenza in Japan. The White House has recently placed pressure on the FDA to allow the unapproved drug to be used for the treatment of COVID-19
ascletis	Aluvia / Pegasys / Ganovo (Ritonavir / PegIFN a1a / Danoprevir)	Marketed	HepC	Hepatitis C NS5A inhibitor	Oral	Apr-2020	Positive results from first clinical study using Ganovo (danoprevir) to treat naive and experienced COVID-19 patients; after a four to twelve day treatment of danoprevir combined with ritonavir, all eleven moderate COVID-19 patients enrolled, were discharged from the hospital
AIM ImmunoTech	Ampligen (Rintatolimod)	Marketed	SARS, solid tumors	TLR2 RNA therapeutic	IV/Nasal	NA	Previously used to successfully treat mice with SARS; Japan's National Institute of Infectious Diseases plans to start testing Ampligen for COVID-19
Roche	Xofluza (baloxavir marboxil)	Marketed	Influenza A & B	Endonuclease inhibitor	Oral	NA	Two hospitals in Shenzhen and Hangzhou have began trials comparing Xofluza (among other drugs) against fapilavir in February
Pharma Mar	Aplidin (plitidepsin)	Marketed	Multiple myeloma	eEF1A2 inhibitor	NA	NA	Positive in vitro study results of Aplidin (plitidepsin) on the human coronavirus HCoV-229E (similar multiplication and propagation mechanism to COVID-19); being tested at the National Biotechnology Centre of the Spanish National Research Council; recently submitted Ph. II trial protocol for patients hospitalized with pneumonia
Johnson & Johnson[1] / GILEAD[2]	Darunavir + Cobicistat	Ph. III	HIV	Protease inhibitor / CYP3A inhibitor	Oral	Dec-2020	Screening for antiviral and vaccine therapies against Coronavirus; currently recruiting for Ph. III trial (n=30), with expected completion by December 30, 2020
GILEAD	Remdesivir	Ph. III	Ebola, Marburg, dengue fever	Prodrug of GS-441524 that targets viral RNA-dependent RNA polymerase	IV	Apr-2020	Being tested in six clinical trials and the company has guided to an initial readout in the next week. Moving from compassionate use to an expanded access program to deal with overwhelming demand. Gilead has significantly ramped up production capacity for remdesivir; with a goal to have delivered 1mm treatment courses by year end. Gilead is also testing HIV drug Truvada (Emtricitabine + tenofovir) to treat COVID-19
ascletis	ASC-09	Ph. III	HIV	Protease inhibitor	Oral	Jun-2020	Asceletis is testing the combination of ASC-09 and Ritonavir in comparison to Lopinavir and Ritonavir in a 160 person trial expected to read out in June 2020; also testing ASC-09 in combination with oseltamivir. ASC-09 was licensed by Asceletis from Johnson and Johnson in mainland China and Macau in 2013
ALGERNON PHARMACEUTICALS	NP-120	Ph. II	Peripheral Circulatory Disorders, IPF	Glu2NB inhibitor	Oral	NA	Algernon announced on March 20, it was retaining Novotech to conduct an investigator-initiated Phase II trial of NP-120 to treat COVID-19

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
Note: Excludes academic studies and company research efforts with no specific drug candidates.
1 Johnson and Johnson is also investigating potential vaccine candidates.
2 Trial run by Shanghai Public Health Clinical Center.

4 Anti-Viral Treatments In Development for COVID-19 (cont'd)

	Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
Repurposed	Innovation Pharmaceuticals Inc.	Brilacidin	Ph. II	Oral Mucositis, IBD, Acute Bacterial and Skin Infections	Defensin mimetic	Oral	NA	Currently being evaluated as both vaccine and therapeutic
Repurposed	BioCryst Pharmaceuticals, Inc.	Galidesivir	Ph. I	Ebola, Zika, Marburg and yellow fever	Nucleoside RNA polymerase inhibitor	IV	NA	In late-stage of development to treat multiple viruses; has shown activity against a wide range of pathogens including coronaviruses
Repurposed	Ridgeback Biotherapeutics / Emory University	EIDD-2801	Preclinical	SARS, MERS, Influenza	Ribonucleoside analog that inhibits viral replication	Oral	NA	Ridgeback plans to quickly advance EIDD-2801 into human trials. EIDD-2801 is a broad-spectrum antiviral that inhibits SARS-CoV-2 and multiple endemic, epidemic and bat coronavirus; tested in mice as both a prophylactic and a therapeutic
Repurposed	Mateon Therapeutics	OT-101	Preclinical	Various Cancers	-	-	NA	Pre-clinical testing demonstrated inhibition of cellular binding, inhibition of viral replication and suppression of viral induced pneumonia
Repurposed	BioSig technologies	Vicromax	Preclinical	Broad spectrum anti-viral		Oral	NA	Demonstrated strong activity against COVID-19 in cell cultures in laboratory testing; already in Ph. I and Ph. II trials for other indications
Novel	sorrento therapeutics /	STI-4920 / CMAB020	Preclinical	NA	Bi-specific fusion protein that binds to the spike protein on SARS-CoV-2	-	NA	Announced a partnership on March 24 to develop and commercialize ACE-MAB. Looking to commence IND enabling preclinical studies in the near future
Novel	sorrento therapeutics	STI-4398	Preclinical	NA	Binds to S1 domain of spike protein on SARS-CoV-2	-	NA	Sorrento produced a preclinical batch of STI-4398 protein to immediately commence testing its neutralization and blocking activity in preventing COVID-19 from infecting ACE-2 cells
Novel	AMGEN / Adaptive	NA	Discovery	NA	Anti-body based anti-viral	-	NA	Adaptive to identify promising antibodies against the coronavirus by analyzing the genetic sequences of immune cells from Covid-19 survivors. Amgen will choose the most promising antibody, or possibly a combination of two or more, to advance into clinical trials.
Novel	e-therapeutics	NA	Discovery	NA	Targeting viral proteins and critical host mechanisms	-	NA	e-therapeutics is collecting and processing COVID-19/host interaction data needed for their Network Driven drug discovery analyses, will have compounds to test within three months. Currently looking for collaborators with screening capability
Novel	Enanta Pharmaceuticals	Anti-virals	Discovery	NA	-	-	NA	Enanta announced in March it would be testing compounds from its antiviral library for potential activity against COVID-19 while also initiating a drug discovery program for direct acting anti-viral mechanisms
Novel	Kamada	Anti-virals	Discovery	NA	-	-	NA	On March 11th, Kamada announced the development of an anti COVID-19 polyclonal immunoglobulin using its IgG platform as a potential treatment for severely ill COVID patients
Novel	VIR / Alnylam	NA	Discovery	NA	RNAi	-	NA	Alnylam selected 350 siRNAs targeting SARS-CoV / SARS-CoV-2 genomes to be screened in *in vitro* potency assays; further evaluation to be led by Vir. Recent agreements expand the companies' existing licensing agreement to now develop up to nine novel siRNAs
Novel	NanoViricides Incorporated	NA	Discovery	NA	ACE-2 virus-binding ligands	-	NA	Has identified candidate ligands in its chemical library targeting the coronavirus host cell receptor ACE-2; planning initial cell culture studies

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
Note: Excludes academic studies and company research efforts with no specific drug candidates.

4 Immune Modulators In Development for COVID-19

Repurposed

Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
Roche	Actemra	Marketed	Castleman disease, arthritis	IL-6 antibody	IV	May-2020	On March 23, the FDA approved a clinical trial to test Actemra in hospitalized patients with severe COVID-19 pneumonia. An additional clinical trial in China expected to enroll 188 patients and be completed by May 10
SANOFI / REGENERON	Kevzara	Marketed	Rheumatoid arthritis	IL-6 antibody	SC	1H 2020	Initiated U.S. Ph. II/III on March 16, 2020 and patients to be enrolled immediately, testing low- and high-doses and multiple efficacy endpoints including fever reduction and reduced supplemental oxygen need. First severe patient outside of the U.S. treated on March 30th
TASLY	T89 (Dantonic)	Marketed	CAD, Hyperlipidaemia, Chronic stable angina	Aryl hydrocarbon receptor (AhR) agonist	Oral	Sep-2020	Currently running trial to evaluate T89 role on oxygen saturation and clinical symptoms in COVID-19 (n=120) with completion by September 15, 2020
青峰医药集团	Xiyanping	Marketed	General viral indications, respiratory tract infections	Plant extract injection	IV	Dec-2021	Current evaluating in a clinical trial to test safety and efficacy of Xiyanping injection in patients with 2019-nCov pneumonia (n=348) with completion by December 14, 2021
Incyte	Jakafi (ruxolitinib)	Marketed	Myelofibrosis/ PCV	JAK inhibitor	Oral, Topical	NA	Novartis and Incyte to initiate Ph. II trial of Jakafi against cases of severe COVID-19 with pneumonia; Jakafi is believed to have potential to treat cytokine storms, severe adverse immune reactions caused by COVID-19
Lilly	Olumiant (baricitinib)	Marketed	Rheumatoid arthritis	JAK inhibitor	Oral	NA	Currently being tested in combination with Ritonavir in a 60 person non randomized open label trial in patients with mild to moderate COVID-19 infection; control group is comprised of patients of similar severity treated with hydroxychloroquine and/or anti-virals
ALEXION	Soliris (Eculizumab)	Marketed	PNH, aHUS	C5 inhibitor	IV	NA	Plans to start a phase II study of Soliris in COVID-19 in the next few days. The study follows a 10-patient proof-of-concept trial in which patients improved in general. Soliris was previously effective in patients with pneumonia and acute respiratory distress syndrome
REGENERON	REGN-EB3	Ph. III	Ebola	Cocktail of multiple antibodies	IV	Apr-2020	Expanded agreement with HHS to develop treatments. Plans to enter clinical testing in early summer and produce hundreds of thousands of doses per month by end of summer
CANFITE BioPharma Ltd	Piclidenoson	Ph. III	Rheumatoid arthritis	A3 adenosine receptor agonist	Oral	NA	Research agreement with Lewis Katz School of Medicine at Temple University to understand Piclidenoson's effect on coronaviruses. CanFite has submitted Piclidenoson for a compassionate use program for COVID-19 patients to the Institutional Review board at Rabin medical center
VANDA PHARMACEUTICALS INC.	Tradipitant	Ph. III	Atopic dermatitis	NK-1 antagonist	Oral	NA	Initiated an FDA approved study of Tradipitant in hospitalized patients with severe COVID-19 pneumonia and ARDS
inflaRx	IFX-1	Ph. III	Hidradenitis Suppurativa, ANCA associated vasculitis	Monoclonal anti-C5a antibody	IV	NA	Dosed first patient into a randomized clinical trial investigating the safety and efficacy of IFX-1 in patients with severe COVID-19-induced pneumonia; positive initial data from licensee treating two COVID-19 patients in China
Ampio PHARMACEUTICALS	Ampion	Ph. II	Osteoarthritis	General anti-inflammatory	IV	NA	General anti-inflammatory being tested in a Phase III trial for osteoarthritis of the knee. Ampio is seeking emergency approval from the FDA to test the drug in 10 COVID-19 patients in Colorado
KINIKSA	Mavrilimumab	Ph. II	Giant cell arteritis, r/r large b-cell lymphoma	Monoclonal antibody (GM-CSFRα inhibitor)	SC	NA	Early data from 6 patients treated with mavrilimumab showed resolution of fever and patients did not need to be put on ventilators; the company plans to evaluate the drug in a Phase II/III trial pending regulatory feedback
CytoDyn	Leronlimab	Ph. II	HIV, GvHD, Breast cancer	CCR5 antagonist	SC	NA	FDA approved Ph. II clinical trial of Leronlimab for COVID-19 treatment in patients with mild / moderate indications; enrollment is to begin immediately. Initial data collected in NY showed severe COVID-19 patients treated with leronlimab had positive results (n=10)
innate pharma	Monalizumab	Ph. II	Various cancers	IgG4 antibody that inhibits the NKG2A receptor	IV	NA	Chinese scientists have found that the number of certain immune cells, T lymphocytes and natural killer cells, decrease significantly in patients with SARS-CoV-2 infection with increased expression of a receptor called NKG2A.

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
Note: Excludes academic studies and company research efforts with no specific drug candidates.

4 Immune Modulators In Development for COVID-19

	Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
Repurposed	PTx	Leukine (sargramostim, rhu-GM-CSF)	Phase I	Neutropenia in AML patients	Bone marrow stimulant	IV	NA	Leukine is being assessed in the SARPAC trial of severe COVID-19 patients with acute hypoxic respiratory failure at University Hospital Ghent
Repurposed	tiziana LIFE SCIENCES	TZLS-501	Preclinical	General inflammatory disorders, RA, MM	IL-6 antibody	-	NA	IL-6 inhibiting monoclonal antibody using proprietary formulation technology
Novel	allo Vir / Baylor College of Medicine	NA	Discovery	NA	SARS-CoV-2 specific T-cell therapy	IV	NA	Allovir and the Baylor College of medicine partnered to develop allogeneic, virus specific T-cell therapies to combat SARS-CoV-2
Novel	Lilly / AbCellera	NA	Discovery	NA	SARS-CoV-2-binding antibodies	-	NA	Co-developing antibodies for COVID-19 (leveraging AbCellera's rapid pandemic response platform). Aiming to have antibody in clinic within four months
Novel	Biogen / VIR	NA	Discovery	NA	Monoclonal antibody	-	NA	Signed letter of intent on March 12; began development work while still finalizing agreement, in which Biogen will further develop Vir's proprietary antibodies
Novel	Takeda	Tak-888	Discovery	Various viral respiratory infections	Anti-SARS-CoV-2 IVIG polyclonal antibodies	-	NA	Plasma-derived therapy has previously been effective in the treatment of severe acute viral respiratory infections; possibly expedited clinical development
Novel	Cel-Sci / University of Georgia	NA	Discovery	NA	Stimulates protective cell-mediated T cell responses and reduces viral load	-	NA	Signed a collaborative research agreement with the University of Georgia to leverage Cel-Sci's LEAPS peptide technology to use conserved regions of coronavirus proteins to induce protective cell-mediated T-cell responses and decrease viral load
Novel	GigaGen	NA	Discovery	NA	Anti-SARS-CoV-2 polyclonal antibodies	-	NA	Developing a treatment called rCIG (recombinant anti-coronavirus 19 hyperimmune gammaglobulin) that will contain antibodies to shut down replication of the SARS-CoV-2 virus; to be given primarily as a therapeutic, but could also potentially be used as a prophylactic
Novel	VIR	NA	Discovery	NA	Monoclonal antibodies	-	NA	As of March 25th, Vir identified multiple neutralizing antibodies against SARS-CoV-2 which could function both prophylactically and therapeutically. Vir intends to test the antibodies in human trials in the next 3 to 5 months. Collaborating with WuXi Biologics; phase 1 data anticipated in ~1 year
Novel	generation bio / VIR	NA	Discovery	NA	Monoclonal antibodies / Non-Viral gene therapy platform	-	NA	Established a research agreement to explore the potential for Generation Bio's non-viral gene therapy platform to extend the impact and reach of Vir's current or future human monoclonal antibodies (mAb) against SARS-CoV-2
Novel	VIR / gsk	NA	Discovery	NA	Monoclonal antibodies / functional genetics	-	NA	Established a research agreement to explore solutions for coronaviruses, including SARS-CoV-2, will leverage GSK's expertise in functional genomics and combine their capabilities in CRISPR screening and artificial intelligence to identify anti-coronavirus compounds that target cellular host genes along with Vir's proprietary monoclonal antibody platform

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
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4 Supportive Care and Other Treatments in Development for COVID-19

Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
MERCK	Pegylated interferon alfa-2b	Marketed	Hep C, Melanoma	Type I Interferon made by leukocytes during viral infection	SC	NA	In trials at Wuhan Jinyintan Hospital
TEIJIN	Alvesco (ciclesonide)	Marketed	Asthma, hay fever	Corticosteroid	Nasal	NA	Japan's National Center for Global Health and Medicine (NCGM) is planning a clinical trial for Teijin's Alvesco (ciclesonide), an inhaled corticosteroid for asthma, for the treatment of pre-symptomatic patients infected with COVID-19
Generic	Alinia (Nitazoxanide)	Marketed	Parasite caused diarrhea	Viral protein expression inhibitor	Oral	NA	Being considered as a potential treatment for COVID-19 because of its potential to inhibit viral protein expression
Roche	Activase (alteplase)	Marketed	Heat attacks, pulmonary embolism, stroke	Binds to fibrin in a thrombus and initiates fibrinolysis	IV	NA	Activase, which was approved by the FDA in 1987 is being evaluated by Roche to determine whether a tissue plasminogen activator could help patients who need a ventilator but can't get access
CytoSorbents	CytoSorb	Marketed	Organ failure due to inflammation	Extracorporeal cytokine adsorber	Hemo-dialysis	NA	Blood purification system that has the potential to be used to mitagate the cytokine storm exhibited in COVID-19 patients; helps physicians control severe inflammation while also helping to reverse shock, and improve respiratory and other organ function
mesoblast the regenerative medicine company	Ryoncil (remestemcel-L)	Filed	Acute GVHD	Allogenic mesenchymal stem cell (MSC) product	IV	NA	Received clearance from the FDA for an IND application to treat patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 with IV infusions of its MSC product candidate remestemcel-L
Bellerophon THERAPEUTICS	INOpulse	Ph. II	Pulmonary hypertension	Inhaled nitric oxide	NODS	NA	Announced that the FDA has granted emergency expanded access to allow INOpulse to be used for the treatment of COVID-19
Healios	HLCM051	Ph. II	ARDS, Stroke	Somatic stem cell regenerative medicine	IV	NA	Enrolling patients in a Phase 2 clinical study in Japan to confirm the safety and efficacy of HLCM051 in pneumonia-induced ARDS patients
vicore pharma	VP01	Ph. II	IPF, Pulmonary fibrosis in systemic sclerosis	AT2R agonist	Oral	NA	Submitted a letter of intent to file a Ph. II clinical trial application for VP01 in COVID-19 patients
NeuroRx / JR RELIEF	Aviptadil (RLF-100)	Ph. II	Erectile Dysfunction, ARDS	Vasoactive intestinal polypeptide	IV	NA	FDA approved a Phase II trial of Aviptadil in the treatment of ARDS in patients infected by COVID-19; NeuroRx and Relief Therapeutics are collaborating to recruit for and execute the Phase II trial
APEIRON BIOLOGICS	APN01	Ph. II	ALI, PAH	Imitates the human enzyme ACE2	IV	-	Randomized, unblinded trial will treat 24 patients for seven days to obtain preliminary data on the impact of rhACE2 on biological, physiologic, and clinical outcomes, as well as safety in patients with severe SARS-CoV-2 infection
Pluristem	PLX Cells	Ph. II	Critical limb Ischemia, Acute Radiation syndrome, others	Placenta-derived MSC like cells; stimulate the body's own regenerative mechanisms	IM	-	Positive preliminary data in COVID-19 patients with acute respiratory failure, 100% survival rate for all seven patients treated with Pluristem's PLX cells. Plans to apply for initiation of multinational clinical trial for treatment of complications associated with COVID-19

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
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4 Supportive Care and Other Treatments in Development for COVID-19

Company	Compound	Phase	Other Target Indications	MoA	Route of Admin.	Catalyst Date	Commentary
celularity / sorrento THERAPEUTICS	CYNK-001	Ph. I	AML, MM	Cell therapy harnessing NK cells to attack cells expressing COVID antigens	IV	NA	Celularity receives FDA clearance for Ph. I/II COVID-19trial of CYNK-001 after Rudy Giuliani endorsement. CYNK-001 is the first immunotherapy cleared for a COVID-19 trial
FARON	Traumakine	Ph. I	Acute Respiratory Distress Syndrome	IFN beta-1a used to prevent capillary leakage	IV	NA	Announced on March 10th that the FDA accepted the proposed protocol design for the use of Traumakine in ARDS patients. Trial will be a pilot randomized and placebo controlled study with approximately 60 patients
ROIVANT SCIENCES	Gimsilumab	Ph. I	Acute Respiratory Distress Syndrome	Anti-GM-CSF Monoclonal Antibody	IV	NA	Seeking FDA approval to rapidly advance the clinical development of gimsilumab for the treatment of ARDS associated with severe acute respiratory syndrome SARS-CoV-2 infection
WINDTREE THERAPEUTICS	KL4 Platform	Preclinical	Acute lung injury	Improves surface tension of pulmonary fluids, preventing alveolar collapse	Aerosol delivery system	NA	Planning to study its KL4 surfactant to mitigate the pulmonary effects of severe COVID-19 infection. Currently pursuing non-dilutive opportunities to fund the project. Approved in liquid dose form for RDS in premature infants
Moleculin / UTMB	WP1122	Preclinical	Glioblastoma, Pancreatic Cancer	Glycolysis and Glycosylation inhibitor	-	NA	Moleculin entered into agreement with University of Texas Medical Branch to pursue research on Moleculin's molecular inhibitors (including WP1122) for antiviral properties and against coronavirus
Mallinckrodt	INOmax	Preclinical	Resp. failure assoc. with pulmonary hypertension	Inhaled nitric oxide	NODS	NA	In early discussions with FDA to submit pre-IND package for use of inhaled nitric oxide (iNO) in coronavirus-associated acute respiratory diseases
BioXyTran Inc.	BXT-25	Preclinical	Stroke	Oxygen transport	IV	NA	On February 6, Bioxytran announced plans to develop its investigational candidate, BXT-25, to treat late-stage patients infected with the new coronavirus who have acute respiratory distress syndrome (ARDS)
汉密顿生物	NA	Preclinical	NA	Umbilical cord-derived MSCs	IV	NA	Wuhan Hamilton is investigating human umbilical cord-derived MSCs for the potential treatment of COVID-19; in February 2020, a clinical trial was planned in China
beroni	NA	Discovery	NA	Precision driven treatment	-	NA	Expecting to commence animal trials of a rapid detection method and precision driven treatment for COVID-19 in March and begin clinical trials as soon as April 2020

Source: EvaluatePharma, FactSet, Company information, equity research, ClinicalTrials.gov and news articles.
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