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COVID-19: Current State of Play

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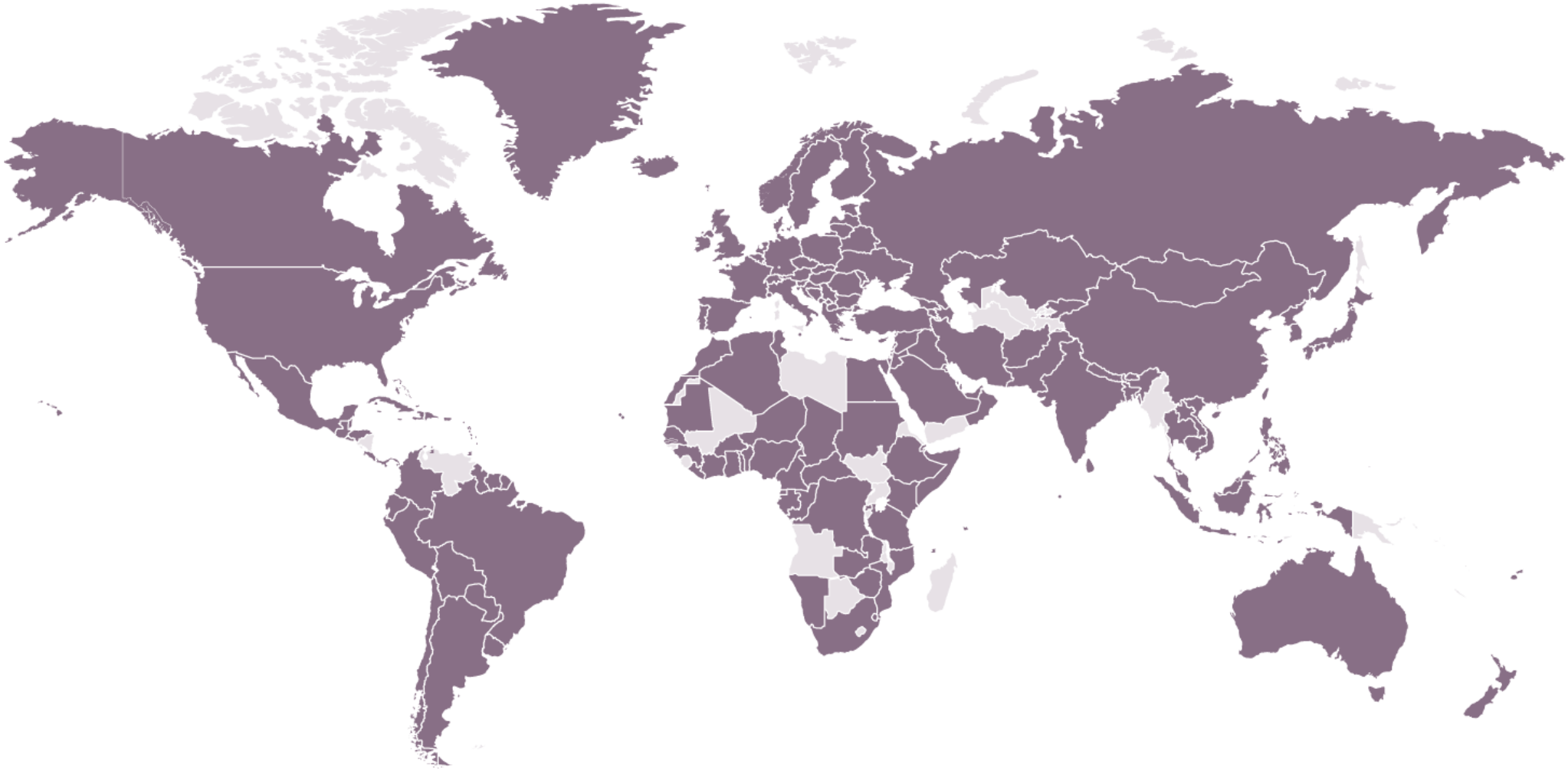
The new Coronavirus has made its presence known globally

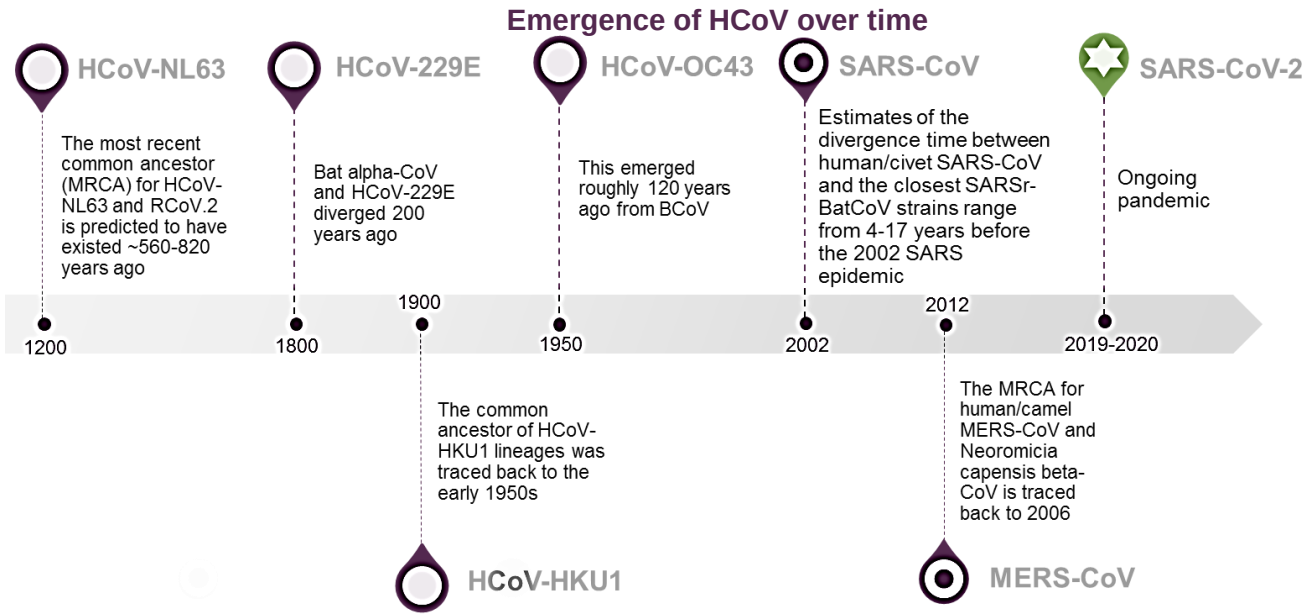


Source: WHO data as of 03/24/2020; adapted from CDC.gov by Guggenheim Securities

A Race Against Time

Coronaviruses, responsible for SARS, MERS and the ongoing COVID-19 outbreaks, changed our lives as we know it

- **Coronaviruses aren't new; they were discovered in the 1960s.** The earliest discovery was a virus causing bronchitis in chickens, and then two more viruses of the same family were discovered in humans causing common cold symptoms. In humans, they can cause mild respiratory infection with symptoms similar to the common cold, but infections from some types can develop into lethal pneumonia (such as SARS-CoV-2) in some patients. In cows and pigs, coronavirus typically causes intestinal disease, manifesting as diarrhea, while in birds it causes respiratory illness.
- **Increased interaction between humans and wildlife increases the risk of zoonotic viruses to evolve with enhanced virulence.** Case in point, the 2002 SARS virus emerged in China from bats, moving to civets and finally to humans. Ten years later, the MERS CoV also emerged from bats, transferring to dromedary camels in the Middle East and then to humans. The new coronavirus, SARS-CoV-2, responsible for causing COVID-19, emerged in China by way of animals in a live market in Nov 2019, and was declared a pandemic by WHO in March 2020.
- **Bats seem to be the natural reservoirs of the current coronavirus**, per the WHO and Zhou et al, 2020, however, the virus seems to have mutated along the way through the animals that are speculated to have transmitted them – civets, pangolins, racoon dogs – recognized as intermediate hosts for the zoonotic transmission of SARS-CoV-2 between bats and humans.
- **Are we the intermediate hosts of SARS-CoV-2?** The answer remains unknown for now since the virus is fairly new in its appearance.



Source: Adapted from Forni et al, 2016, by Guggenheim Securities

There are over 36 different types of Coronavirus

There are over 36 different types of CoVs that infect, humans, other mammals and birds

They can be categorized into different sub-types: alpha, beta, gamma and delta, based on their phylogenetic clustering -

- Alpha and beta sub-types infect mammals
- Gammacoronaviruses infect avian species
- Deltacoronaviruses infect both mammals and avian species

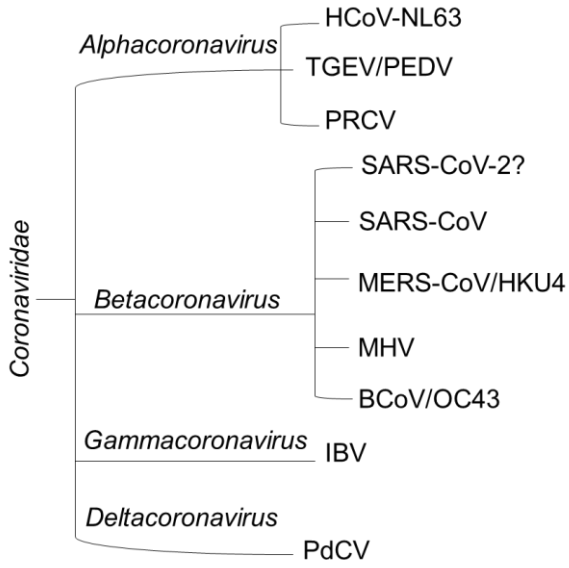
To date, there are 7 types of coronavirus that are known to infect humans. Four low pathogenicity coronaviruses endemic in humans include 229E, NL63, OC43 and HKU1.

While common human coronaviruses typically cause mild symptoms, new types of coronaviruses have shown more severe symptoms and lethality. As noted these novel viruses developed in animals and have adapted to infect humans, developing new virulence traits, causing more severe symptoms and increased lethality rates. To date, no therapeutics or vaccines have been approved against any human-infecting coronaviruses.

Three recent examples of CoVs are -

- MERS-CoV (the coronavirus that causes Middle East Respiratory Syndrome, or MERS)
- SARS-CoV (the coronavirus that causes severe acute respiratory syndrome, or SARS)
- SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)

Classification of Coronaviruses



This multitude of CoVs is a result of their inherent genomic diversity

The high diversity of CoVs is attributed to 3 viral traits –

i) Potentially high mutations rates associated with RNA replication, generally estimated to be in the range of e-3 to e-5 (2e-6 in the case of SARS-CoV), and this rate changes depending on environmental/stress pressures

ii) Recombination frequencies within the CoV family can be as high as 25% during mixed infection, likely resulting from discontinuous RNA transcription and recombination between viral genomes and subgenomic replication complexes

iii) Since CoVs are the largest of RNA viruses, they have an increased opportunity for change and room for modification, which allows the viruses to rapidly adapt to novel hosts (via a plastic surface glycoprotein that tolerates high rates of mutation), ecological niches, tissue tropism, and even generate novel CoVs.

Source: Adapted from Fang Li, 2016, by Guggenheim Securities

Coronavirus Code

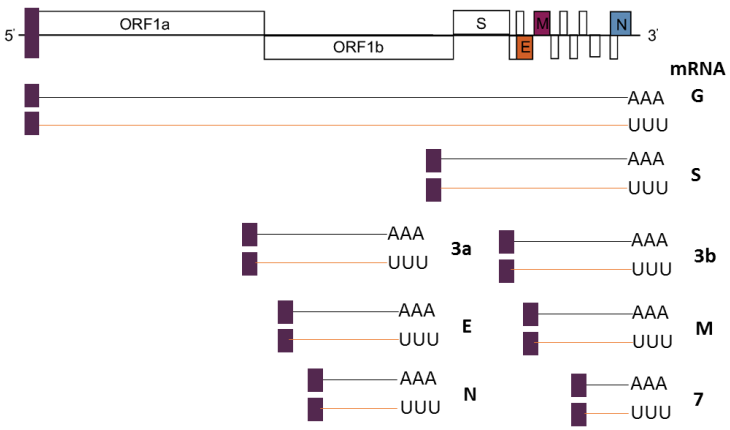
Coronaviruses are part of the Coronaviridae family, within the order Nidovirales, and are enveloped, positive- stranded RNA viruses with a genome of ~ 27kb-32kb, which makes them the largest known RNA viruses

- They have a polycistronic genome organization, which means one mRNA can encode for more than one protein.
- Coronaviruses also use a unique transcription mechanism to produce a set of subgenomic (sg) mRNAs. These sgmRNAs are used to express the open reading frames (ORFs) which are downstream of the replicase ORFs 1a and 1b, encoding structural and accessory proteins. **Basically, coronavirus is a skilled at packing a lot of information into a tiny capsid.**

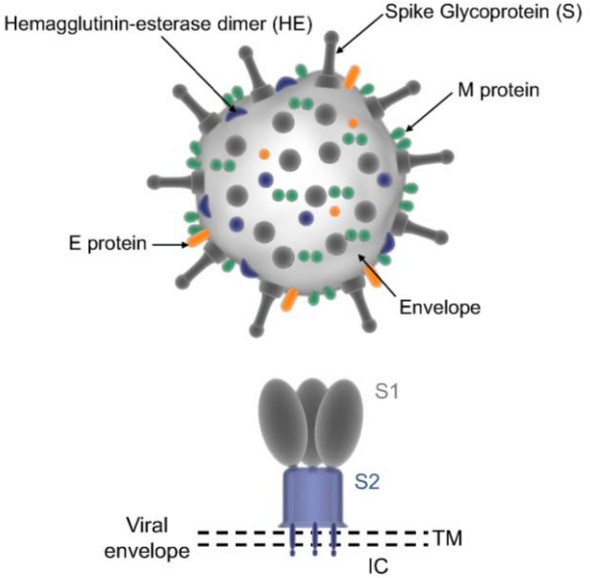
Speaking of capsids, Coronaviruses genomes are contained within a helical capsid, that is surrounded by an envelope

- Coronaviruses are approximately 125nm in diameter.
- The helical capsid is formed by the nucleocapsid protein (N).
- The envelope is composed of three structural proteins: the envelope protein (E) and the membrane protein (M), which are involved in membrane assembly, and the spike protein (S), which mediates viral entry into cells. Some coronaviruses also encode for an envelope-associated hemagglutinin-esterase protein (HE), which binds to sialic acid on host glycoproteins and is thought to promote viral entry into host cells and viral spread through the mucosa.
- The S protein forms long projections from the envelope of the virus, giving the virus a crown-like appearance, hence the name “Coronavirus” (Corona in latin means crown).
- The spike protein consists of three segments: a short intracellular tail, a large ectodomain and a single-pass transmembrane anchor.
- The ectodomain contains two units – i) Receptor-binding subunit S1: This subunit binds to host receptors to mediate viral attachment, and ii) Membrane fusion subunit S2: This subunit fuses the viral and host membrane, allowing viral genomes to enter host cells.

Coronavirus genome ORFs



Coronavirus structure (top) and the ectodomain of the Spike glycoprotein (bottom)



Source: Adapted from Wilde et al, 2017, Holmes K, 2003, and , Fang Li, 2017, by Guggenheim Securities

The Skeleton of SARS-CoV-2

SARS-CoV-2's genome resembles a typical CoV genome (detailed earlier), with a single stranded, positive-sense RNA

- The virus belongs to the group of betacoronaviruses that also includes bat-SARS-like (SL)-ZC45, Bat-SL ZXC21, SARS-CoV, and MERS-CoV. On nucleotide sequence homology, the new virus is 96% identical to the bat coronavirus isolate RaTG-13.Phylogenetically, CoV-2 is closely related to bat-SL-CoV ZC45 and bat-SL-CoV ZXC21 and more distantly related to the SARS-CoV.

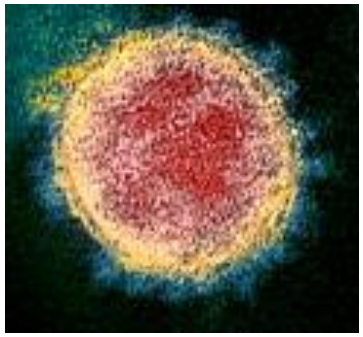
The virus' spiky capsid is the first point of contact with a host cell

- A CoV-2 virion is ~50-100nm in diameter, composed by the virus' four structural proteins - S (spike), E (envelope), M (membrane), and N (nucleocapsid), like other coronaviruses detailed previously. The N protein forms the physical "shell" holding the RNA genome, and the S, E, and M proteins form the viral envelope.
- The ~1200 amino acid long spike protein (S) is now believed to be the protein that helps the virus latch onto the host cell membrane to start the process of infection (detailed in the next slide). This is important from the perspective of virus-host cell receptor binding, tissue tropism and pathogenesis.

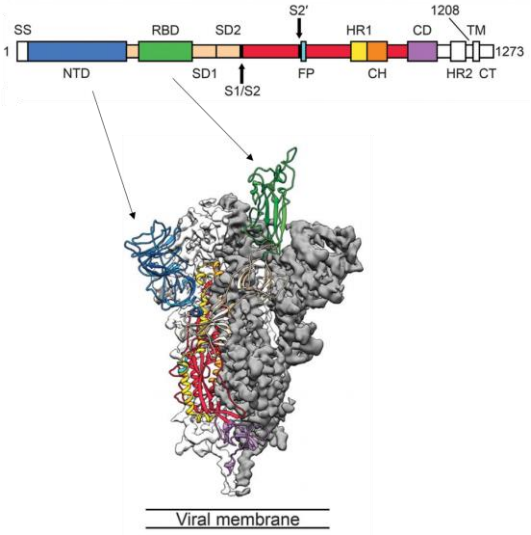
Spike protein's RBD and furin cleavage site enabled SARS-CoV-2 to become a zoonotic virus (one that can spread between animals and people)

- The coronavirus's receptor binding domain (RBD, the region that binds to a specific receptor on the host cell) in the S1 subunit of S is the most variable part of the viral genome. RBD mutations in the circulating CoV-2 strain have conferred additional structural stability and infectivity to the S protein.
- The S2 subunit (with the internal fusion peptide, IFP, that enables viral entry) has a furin cleavage sequence (PRRARS|V) which is activated in the presence of the protease furin. The addition of a leading proline (PRRA) in this region results in an O-linked glycosylation of S673, T678 and S686 around the site, making it unique to this new virus. On a side note, the closely related RaTG-13 bat CoV does not have the furin cleavage site. It is noteworthy that the insertion of this site in the HA glycoprotein of the highly pathogenic avian H5N1 influenza viruses contributed to higher pathogenicity and enhanced cellular tropism.
- Coutard et al, 2020, speculate that a "gain-of-function" with the furin cleavage site allowed a bat CoV to gain the ability to infect humans, attacking the respiratory system specifically as furin is highly expressed in the lungs (and in the liver and small intestines). The new virus possibly exploits this convertase to activate its spike protein, per the research group. Interestingly, this site is processed on viral egress in the case of MERS-CoV S and on endocytosis in SARS-CoV S.

TEM image of SARS-CoV-2 isolated from a clinical sample



Structure of the spike protein of SARS-CoV-2



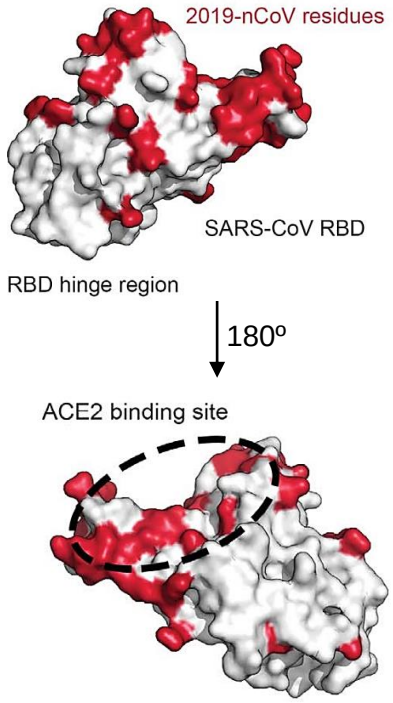
Source: Adapted from NIH.gov and Wrapp et al, 2020, by Guggenheim Securities

SARS-CoV-2 latches onto the angiotensin-converting enzyme 2 (ACE2) receptor to gain entry into cells

SARS-CoV-2 binds to the ACE2 receptor more tightly compared to the SARS-CoV

- CoV receptor interactions are key determinants that regulate host range, cross-species transmission, and tissue tropism. SARS-CoV-2 uses its densely glycosylated spike (S) protein to enter the cells, which is triggered by the binding of the S1 subunit to the receptor.
- Studies in 2003 had identified ACE2 to be the host cellular receptor for the SARS-CoV, and it turns out the same receptor is also the entry point for CoV-2. The virus also uses host protease TMPRSS2 to prime its entry into the cells by cutting open the spike protein to expose the fusion peptide.
- The S1 subunit's RBD allows the virus to directly bind to the peptidase domain (PD) of ACE2. The S2 subunit is thought to play a role in membrane fusion. Hence, the S spike is critical for not only the attachment of the virus to the host cell surface, but also the fusion of viral and host cell membranes to allow the infection to start.
- Additionally, the ACE2 receptor is active in a dimer form. Hence, the resulting two peptidase domains are able to bind to two SARS-CoV S spikes simultaneously.
- While the SARS-CoV-2 S shares a ~76% and a 80% amino acid identity with SARS-CoV and CoV ZXC21 respectively, Wrapp et al, 2020, showed that the RBD of SARS-CoV-2 is different from other SARS-CoV RBDs (hotspot variants in the binding site), which enables a tighter a complex formation with ACE2 **resulting in ~10-20x higher binding affinity when compared to the SARS-CoV**. This enhanced affinity to the receptor may be a critical factor in increasing CoV-2 virus infectivity and human-to-human transmission vs. other CoVs, though this has yet to be proven.
- The knowledge of these receptors is important from the perspective of a potential antiviral intervention against these targets, for example, ACE2/ TMPRSS2 inhibitors or the use of decoy ligands/antibodies against spike proteins/CD147 or serum from convalescent SARS patients to neutralize CoV-2-S-driven entry (more on these later).

SARS-CoV-2 RBD residue variations (in red), superimposed on the SARS-CoV RBD (in white)



CD147 – another door to cellular entry?

- Wang et al, 2020, noted that CoV-2 could also use the CD147 receptor/basigin to invade host cells.

Target cells

- Cells that express ACE2 include alveolar type 2 (AT2) cells (cells responsible for surfactant biosynthesis and self-renewal) in the lungs, esophagus upper and stratified epithelial cells, lymphocytes within the mucosa of oral cavity and epithelial cells of the tongue, absorptive enterocytes from ileum and colon (most vulnerable intestinal epithelial cells), cholangiocytes (epithelial cells of the bile duct), myocardial cells, kidney proximal tubule cells, and bladder urothelial cells.

Source: Adapted from Wrapp et al, 2020, by Guggenheim Securities

Summary of SARS-CoV-2 Lifecycle

Viral attachment

- The initial attachment of the CoV-2 with host cells begins with S-protein mediated interaction with a host receptor. S protein is split into S1/S2, because those two sub-units mediate the distinct tasks of attachment and entry, respectively.
- The interaction between the S1/RBD and the host receptor promotes receptor mediated endocytosis, allowing for viral entry into the host cell.

Viral entry

- Once viral attachment and entry in an endosome is established, the virus must gain access to the host to begin the infection. For this to occur, the first cleavage separates the RBD and the fusion domain of the S protein at viral attachment. This is followed by a second cleavage at the S2' site that exposes the fusion peptide (FP) after splitting it from the internal fusion peptide (IFP). It is believed that both FP and IFP participate in the viral entry process.
- Generally, in CoVs, a cleavage at S2' allows the FP to insert into the membrane of the acidified endosome and then two heptad repeats of S2 join to form an antiparallel six helix bundle. This formation promotes mixing of viral and host membranes, resulting in fusion and release of the viral genome into the cytosol.

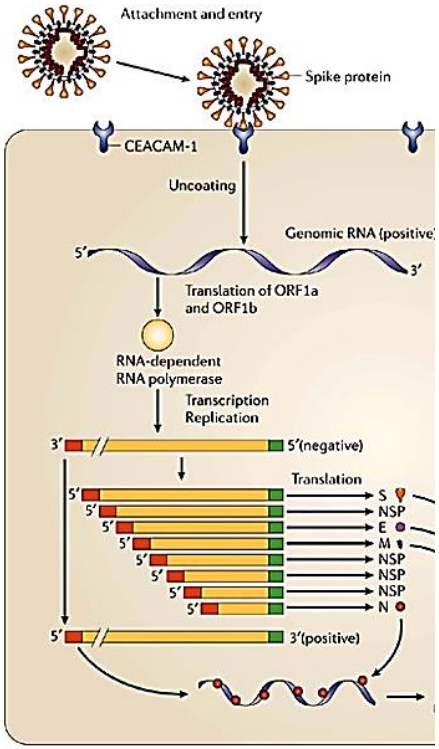
Viral modulation of host innate immune responses

- Importantly, SARS-CoV-2 dampens the type 1 IFN pathway and delays immune recognition (more on this in the following slides).

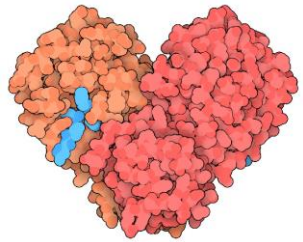
Viral replication

- Upon infecting the cell, SARS-CoV-2 genome directs the synthesis of two long polyproteins that include the machinery the virus needs to replicate new viruses (as explained earlier). These proteins include a replication/ transcription complex that makes more RNA, several structural proteins that construct new virions, and two proteases. The proteases cut the polyproteins into the above mentioned functional pieces.
- The protease of CoV-2 is a 33.8kDa main protease (Mpro), also referred to as the 3C-like protease. Structurally, the enzyme is a dimer of two identical subunits that together form two active sites. The protease also has a peptide-like inhibitor bound in the active site (shown in the figure on the right).
- Inhibition of Mpro could potentially help in the inhibition of viral replication.

Lifecycle of SARS-CoV as reference – part I



Main protease (Mpro) of SARS-CoV-19; the inhibitor is shown in blue



Source: Adapted from Stadler et al, 2003, and the Protein Data Bank (PDB) by Guggenheim Securities

Summary of SARS-CoV-2 Lifecycle (contd.)

Viral translation

- To our knowledge the lifecycle of SARS-Cov-2 is not fully elucidated. However, historically, we know that in CoVs, following the replication of viral particles/genome and subgenomic RNA synthesis, the viral structural proteins, S, E, and M are translated and inserted into the endoplasmic reticulum.

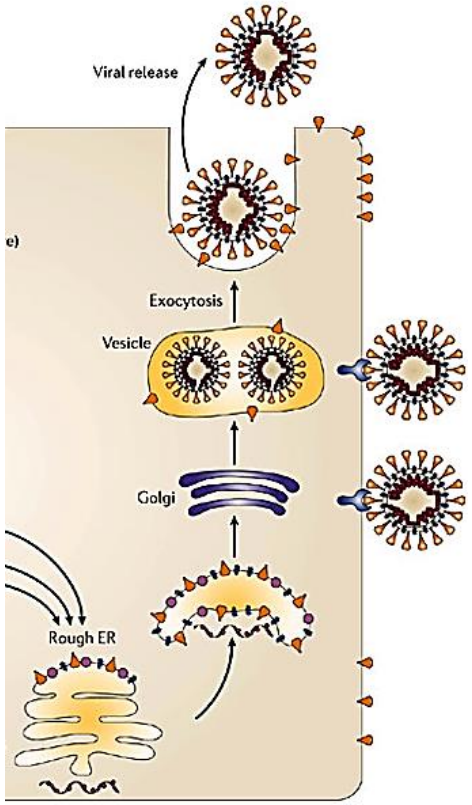
Viral assembly

- Most protein-protein interactions during CoV assembly are driven by the M protein. Addition of E protein expression produces viral envelopes, while the N protein enhances virus-like particle formation. The S protein is not required for assembly, but is incorporated into the virions at a critical step after it interacts with the M protein in the ER-Golgi intermediate compartment.
- Moving along the secretory pathway into the ER-Golgi intermediate compartment, the viral genomes are encapsidated by the N protein and bud into membranes containing viral structural proteins, forming mature virions.

Viral egress

- After the virions are assembled, they are transported to the cell surface in vesicles and released by exocytosis. It is reported that in several CoVs, the S protein that is unincorporated into the viral particles reaches the cell surface where it enables cell-cell fusion between infected cells and adjacent, uninfected cells. This results in the formation of giant, multinucleated cells that allow the virus to infect additional cells, undetected or neutralized by antibodies.

Lifecycle of SARS-CoV as reference – part 2



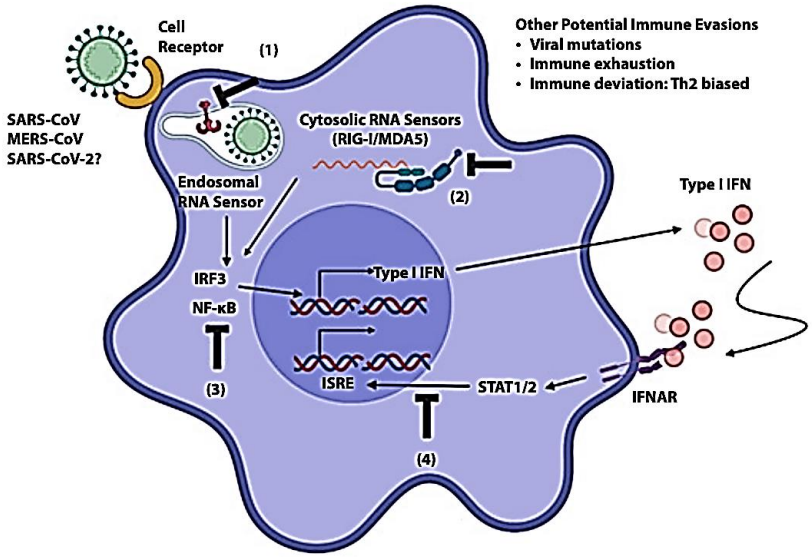
Source: Adapted from Stadler et al, 2003, by Guggenheim Securities

Like Other CoVs, The New Virus Has Mastered Its Immune Evasion Technique

SARS-CoV-2 modulates the host innate immune response

- Recent reports suggest that SARS-CoV-2, and other CoVs in general, have adapted to evade the immune system and dampen immune responses, which could partially explain the prolonged incubation period (2-11 days) vs. the seasonal flu (1-4 days). Sharing the same genus, SARS-CoV-2 is thought to escape from the immune system in ways similar to those deployed by SARS-CoV and MERS-CoV – i) interference of viral RNA sensing; ii) inhibition of type I interferon (IFN) recognition and signaling; iii) delaying/dampening of STAT1/2 activation downstream of IFN/IFNAR, which in totality affects adaptive immune activation.
- A group of researchers from the University of Chicago and its collaborators recently identified a newly mapped protein called Nsp15 on the virus. This protein is conserved among coronaviruses; the one in SARS-CoV-2 is 89% identical to the one in SARS-CoV. Nsp15 is essential for the virus' lifecycle and virulence, and while up until recently it was thought to be a direct participant in viral replication, new studies have elucidated a different role – host immune response modulation to enable viral replication. Its important to note that early studies with Nsp15 inhibitors on SARS-CoV in 2010 had demonstrated that they can slow viral replication, and researchers now suggest that this protein could be a novel target for drug development for CoV-2.

Potential mechanism of IFN downregulation by SARS-CoV-2



- Gordon et al, 2020, mapped out the viral-host protein-protein interactome and illustrated that several viral proteins impact host innate immune responses. Nsp13 was found to interact with TBK1 and TBKBP1/SINTBAD of the IFN pathway, while also modulating the NFKB inflammatory signaling. Nsp15 modulates IFN type 1 response, whilst Orf6 antagonizes host IFN signaling. Additionally, the viral N protein possibly suppresses host stress granules and shuts off their translation. It targets G3BP1, an essential antiviral, stress granule protein that induces an innate immune response through multiple mechanisms. These granules are typically induced upon recognition of viral dsRNA. Inhibition of these highlighted pathways through new or repurposed drugs such as rapamycin which inhibits mTOR and reduces MERS infection by 60% in vitro could be explored for an antiviral intervention for SARS-CoV-2.

SARS-CoV-2 could also potentially modulate the host adaptive immune response

- A prolonged persistence of the virus may help exacerbate inflammatory responses that could lead to immune exhaustion and immune suppression, per Prompetchara et al, 2020.
- While CoV-2's adaptive immune evasion strategy is not well studied presently, parallels could be cautiously drawn from the MERS-CoV infection of macrophages or dendritic cells, where the virus was shown to downregulate antigen presentation via MHC class I and MHC class II, resulting in markedly diminished T cell activation.

Source: Adapted from Prompetchara et al, 2020, by Guggenheim Securities

SARS-CoV-2 Is Contagious, But Is Not Airborne

SARS-CoV-2 predominantly spreads through respiratory transmission

- The main route of transmission is via respiratory droplets and/or contact. As far as we have been able to tell/read, there has been no evidence of aerosol/airborne transmission. The virus is now known to remain stable in aerosol and on various surfaces for hours-days.
- Reports have reported detection of the virus in feces of confirmed patients (in both China and the US), suggesting possible fecal-oral transmission. It remains unclear whether eating virus-contaminated foods could led to infection and/or transmission. The risk of viral transmission through blood transfusions is presently theoretical.
- Maternal to fetal infection also appears possible, based on a report of a positive mother birthing a newborn who also tested positive for viral nucleic acid ~30h after birth.

The WHO estimates SARS-CoV-2 to have an R0 of 2.0-3.9

- R0 or the reproduction number, or R0 is the scale to define the infectivity of a virus. The R0 is the average number of other people that one infected person will infect, in a completely non-immune population.
- To put things in perspective, the R0 of SARS, MERS, seasonal flu, and measles is <1-2.75, ~1, 1.3 and 11-18, respectively.
- Early data from the first 425 cases in Wuhan suggested an R0 of 2.2.

Should we be worried about virus mutations during the pandemic? These reports don't suggest so.

- According to the WHO-China Joint Mission on COVID-19 Report, significant mutation of the virus have not been observed over time/across geographies; whole genome sequencing of 104 strains isolated from patients in different locations (with symptoms onset from Dec 19 to Feb 20) showed 99.9% homology.
- Interestingly, Grubaugh et al, 2020, detail that although RNA viruses are highly prone to accumulating mutations during every copying cycle because of an intrinsically error-prone RNA polymerase for replication, stringent evolutionary constraints don't allow them to do so unless the mutations give an epidemiologically selective advantage(s) in terms of transmission and virulence. As such, the authors think it is unlikely that viral adaptation in humans will result in newer (potentially more dangerous) strains.
- This line of thought is also supported by latest ongoing studies where researchers have noted that the virus has thus far maintained overall fitness, exhibiting only 4-10 genetic differences between the US and Wuhan strains. This could be attributed to the virus' exonuclease, which has a proofreading machinery that helps reduce the error / mutation rate. This also suggests to the scientists that a potential vaccine for SARS-CoV-2 would be a single vaccine to confer durable, long-term immunity, unlike the annual vaccination needed for influenza.
- However, we'd highlight that Tang et al, 2020, who studied 103 SARS-CoV-2 genomes, found that the new strain of the virus evolved into two major types – strains L and S – defined by two different but tightly linked SNPs. Although the L strain is more prevalent of the two (~70%) and was predominant in the early days of the outbreak in Wuhan, its frequency decreased after Jan 2020. The research group speculates that the L strain might be more aggressive and spreads quickly, but human intervention has likely placed a more severe selective pressure on it. In comparison, the S strain is evolutionarily older (ancestral), less aggressive and may have increased in relative frequency due to a relatively weaker selective pressure, per the group.

COVID-19 Clinically Manifests as a Range of Mild To Severe Acute Respiratory Distress Syndrome (ARDS)

Incubation period is estimated to range from 1-12.5 days, with a median of 5-6 days

- WHO guidance estimates 14 days, with symptoms appearing an average of 5-6 days after infection (including mild respiratory symptoms and fever).

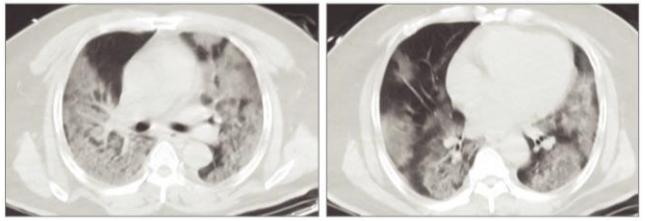
Signs and symptoms

- The clinical symptoms of COVID-19 are similar to those of SARS and MERS – fever, fatigue, respiratory symptoms such as sputum production, dry cough, shortness of breath, sore throat, nasal congestion, and others such as headache, myalgia / arthralgia, chills, nausea, diarrhea, hemoptysis and conjunctival congestion. In some cases, digestive symptoms seem to become more pronounced as the severity of the disease increases.
- Recent reports show that lymphopenia and cytokine release syndrome (CRS) are also important clinical features in patients with severe SARS-CoV-2 infection.
- It is important to note that, based on hospitalized patient data, ~80% of positive cases are mild-moderate (most of which recover), 13.8% have a severe disease, and 6.1% are critical cases, according to the WHO-China Report. The severity and fatality rate of COVID-19 are reportedly milder than that of SARS and MERS.
- On that note, the mortality rate of COVID-19 worldwide is ~4.43% (as of 03/25/2020), and is caused by a multi-organ failure especially in the elderly and people with underlying health conditions such as hypertension, cardiovascular disease, cancer and diabetes. Children seem to have a much milder disease than adults; scientists currently do not know why.

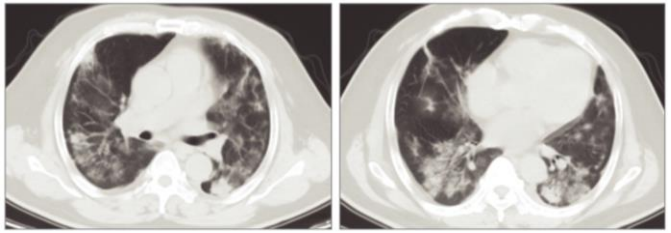
Clinical course

- Per the CDC, the clinical presentation is very variable, with some patients experiencing a mean time of 9 days from illness onset to hospital admission with pneumonia, while some subset of patients had a median time of 8 days from symptom onset to ARDS. Although clinical deterioration may be seen during the second week of illness, not all patients develop a severe or fatal COVID-19.
- Around 20-30% of COVID-19 patients hospitalized with severe symptoms and/or pneumonia require ventilator support.

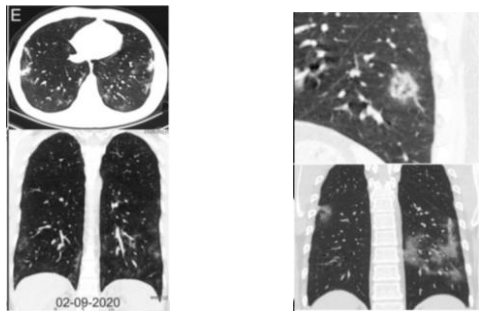
Chest CT of a 52 year old COVID-19 patient 5 days after the onset of symptoms shows ground glass opacity in both lungs



Chest CT of a 52 year old COVID-19 patient 19 days after the onset of symptoms and treatment with oxygen therapy



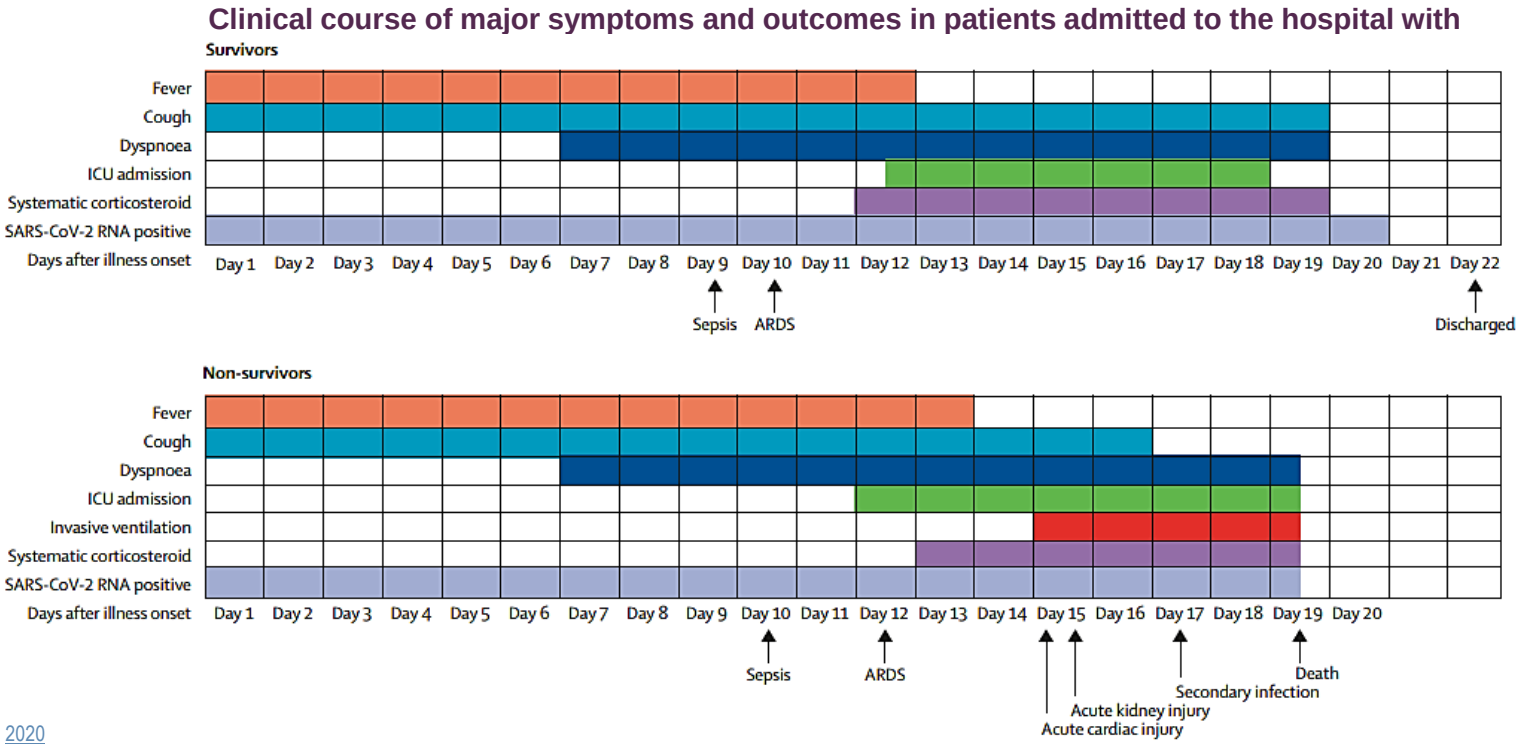
Chest CT of a (left) 29yo COVID-19 patient with fever for 6 days, ground-glass opacities and pneumonia; (right) 34yo patient with fever for 4 days, ground-glass opacities and early pneumonia



Source: Adapted from Wang et al, 2020, and Ai et al, 2020, by Guggenheim Securities

Clinical Course of the Immune Responses to SARS-CoV-2

- In a retrospective study of 191 COVID-19 patients, Zhou et al, 2020, found that older age, d-dimer levels (>1µg/mL on hospitalization; this blood protein lingers around after blood clot has been degraded), and a high Sequential Organ Failure Assessment (SOFA) score were risk factors associated with poor prognosis and increased odds of in-hospital death.
- We'd highlight that in the study above, surviving patients had a significantly higher level of baseline lymphocyte vs non-survivors; their lymphocyte count was lowest on day 7 after the onset of illness and improved during hospitalization, while non-survivors had severe lymphopenia until their death. The latter group also had elevated levels of d-dimer, high-sensitivity cardiac troponin I (which increased rapidly from day 16 after disease onset), serum ferritin, lactate dehydrogenase (LDH), and IL-6 throughout the clinical course. Of note, LDH increased for both survivors and non-survivors in the early stage of sickness, but decreased from day 13 for survivors.
- In 137 survivors, the median time from illness onset to fever was 1 day (median duration of 12 days), to cough was 1 day (median duration of 12 days), to dyspnea was 7 days (median duration of 13 days), to sepsis was 9 days, to ARDS was 10 days, to discharge was 22 days. Acute cardiac and kidney injury and secondary infections developed following sepsis and ARDS in 1 patient.
- In 54 non-survivors, the median time from illness onset to fever was 1 day (median duration of 12 days), to cough was 1 day (median duration of 12 days), to dyspnea was 7 days (median duration of 13 days), to sepsis was 10 days, to ARDS was 12 days, to death was 18.5 days. Acute cardiac and kidney injury and secondary infections developed following sepsis and ARDS in 27-32 patients.



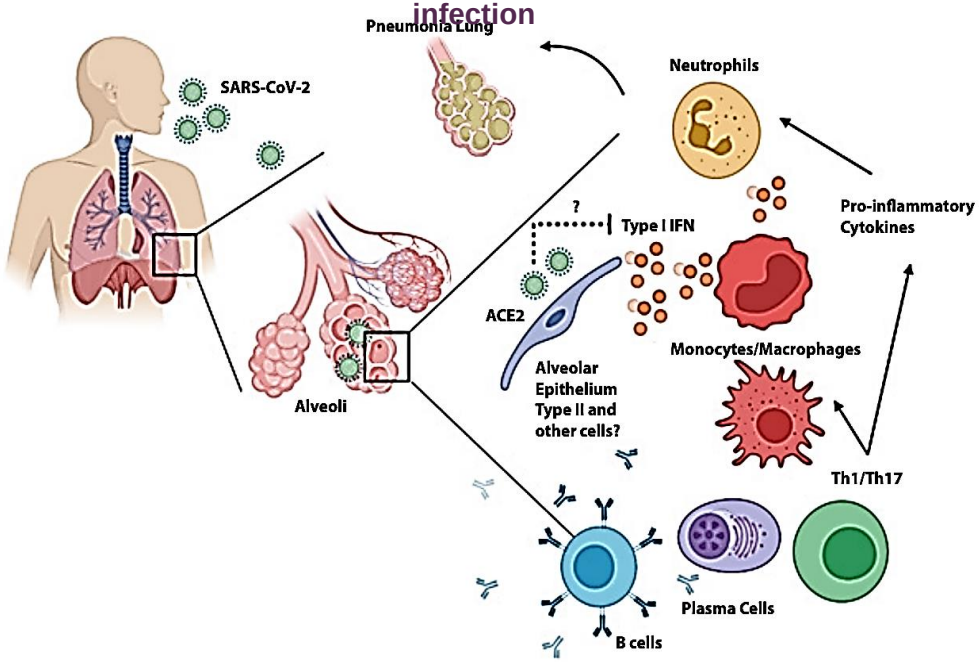
Source: Zhou et al, 2020

Potential pathology mechanism is believed to be viral replication, immune hyperactivity, and pulmonary destruction

Pathology

- Molecular pathology is presently not well studied, but is hypothesized to consist of three phases: viral replication, immune hyperactivity, and pulmonary destruction.
- In the lungs, the disease causes diffuse alveolar damage (cilia are shed), epithelial cell proliferation, and an increase of macrophages, producing a characteristic pulmonary ground glass opacity on chest CT.
- The disease could also be accompanied by lymphopenia and hemophagocytosis that could result in CRS in severe COVID-19, with some patients reporting high levels of proinflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα. Increased levels of immune regulatory molecules and decreased levels of multiple cytokines in peripheral blood T cells have been noted in severely diseased patients and may help predict the progression to pneumonia in COVID-19 patients.
- CRS kicks off viral sepsis and inflammatory-induced lung injury which may lead to other complications such as pneumonitis, ARDS, respiratory failure, shock, organ failure and potentially death.
- A case of co-infection with influenza A virus has also been reported in China.

Potential host immune responses elicited by the virus during cellular infection



Viral load and shedding

- Latest reports document high viral loads in the early phase of the disease (peaking around 5-6 days post symptom onset in some patients with e4-e7 copies/mL in throat swab/sputum samples), indicating that patients could be the most infectious during this time period, and could also be transmitting the virus asymptomatically. In another study, a higher viral load was detected in the nose than the throat, while also laying emphasis on the finding that the viral load in the asymptomatic patient evaluated was similar to that in the symptomatic patients. Viral load is also correlated with age; older patients with low immunity and high ACE2 expression have worse outcomes.
- Viral shedding has been reported to last for 8-37 days in COVID-19 survivors, with a median duration of 20 days. Fecal samples from patients have a prolonged presence of CoV-2 RNA, with a study reporting positive samples for 33 days after the respiratory samples became negative in a patient.

Source: Adapted from Prompetchara et al, 2020, by Guggenheim Securities

There Has Been an Uptick in the Number of Tests Coming to the Field

Several diagnostic tests have been FDA-approved for emergency use authorization (EUA) to perform the diagnosis of COVID-19

- After the full genome of the virus was published this year on Jan 10, a group of German scientists developed and refined their first RT-PCR-based diagnostic protocol for COVID-19, to target viral genes unique to the newly discovered virus. Specifically, the test detects the presence of the envelope (E) gene, and the gene for the enzyme RNA-dependent RNA polymerase. The test is reported to have high analytical sensitivity.
- This protocol has since been recommended by the WHO to detect the virus in clinical swabbed samples from the nose and throat. It takes 24-28 hours for a laboratory to obtain a result by this method. At a Sydney lab which uses this test, results were confirmed with whole genome sequencing, viral culture, or electron microscopy.
- On March 21, 2020, the FDA approved an EUA for DHR's subsidiary, Cepheid's, RT-PCR based Cepheid Xpert Xpress SARS-CoV-2 test that provides results in 45 minutes.
- Other FDA-issued tests to diagnose a SARS-CoV-2 viral infection are from Mesa Biotech, BioFire Defense, PrimerDesign Ltd., Abbott Molecular, TMO, Roche Molecular Systems, amongst others which are listed here.
- Currently, the FDA believes that to diagnose symptomatic patients, nasal swabs from just the front of the nose rather than the depth of the nasal cavity, are acceptable and would provide more comfort to patients during sample collection. This could possibly encourage self collection of specimen and is a simpler swab to do.

Other tests in development

- Rheonix Corporation is seeking an EUA from the FDA for its fully automated, microfluidic system-based diagnostic assay.
- A research use only RT-PCR test developed by the CDC targets 3 sequences in the N gene along with the RNA-dependent RNA polymerase gene.
- Another research use only, CRISPR-Cas13-based SHERLOCK protocol developed by the McGovern Institute uses synthetic COVID-19 RNA fragments and RNA guides that recognize two signatures of COVID-19. The test uses paper strips, and has a turnaround time of ~1 hour.
- A group of Taiwanese researchers aim to identify a SARS-CoV-2 antibody that could potentially be used for COVID-19 diagnosis, which could reportedly provide results in 10-15 minutes.
- Heat Biologics and University of Miami are collaborating to develop a proprietary point-of-care COVID-19 test that will use a paper strip to provide results in 30 minutes.

How do we get rid of it?

There are currently no specific antiviral therapies for CoV-2…

- IFN with ribavirin has demonstrated limited efficacy against CoV infection.
- A 2015 meta-analysis of clinical studies of convalescent plasma in severe acute respiratory infections (SARIs) of viral etiology indicates that the therapy was safe and may reduce mortality – though more robust clinical trials are needed.
- Sera from convalescent patients has been shown to neutralize infectivity of isolated COVID-19 virus *in vitro*.
- Interestingly, a mild-to-moderate COVID-19 patient who made a full symptomatic recovery was reported to develop antibody-secreting cells (ASCs), follicular helper T cells (TFH cells), activated CD4+ T cells and CD8+ T cells in addition to IgM and IgG antibodies specific to SARS-CoV-2 before the resolution of her symptoms, and for at least 7 days after recovery. The study group suggests that the characterization of these immune parameters could be used to predict disease severity in patients, adding that early adaptive immune responses could be correlated with better clinical outcomes.

… though several efforts to discover a treatment and/or vaccine for the novel CoV are in development

- There are trials ongoing with several re-purposed drugs or existing methods including remdesivir, chloroquine, favipiravir, convalescent plasma, TCM among others
- Per the WHO-China Report, the ideal animal model for studying routes of SARS-CoV-2 transmission, pathogenesis, antiviral therapy, vaccine and immune responses has yet to be found. The ACE2 transgenic mouse model and Macaca Rhesus model are already used in research laboratories.

In the following slides, we attempt to review ~67 programs in development for COVID-19

- In what is hopefully a comprehensive but brief manner we have summarized the mechanisms and current status of each program/drug, as well as the ongoing clinical trials with each
- Clinical development in this space is obviously evolving rapidly; the following slides represent a snapshot of the landscape as of ~3/22/20
- In addition to the following slides, we also put together an excel based tracker – let us know if you'd like a copy.

Small Molecules for the treatment of COVID-19

1. Chloroquine / Hydroxychloroquine
2. Direct Acting Antivirals (DAAs) e.g. remdesivir, favipiravir (among others)

Chloroquine (CQ) / Hydroxychloroquine (HCQ)

Background and Mechanism

Chloroquine (CQ) is a 4-aminoquinoline, synthetic quinine, with anti-inflammatory activity with the potential for chemosensitization and radiosensitization activities.

It has been used as an anti-malarial drug since the 1940's. The mechanism behind chloroquine activity as an anti-malarial has still not been elucidated.

Hydroxychloroquine (HCQ) is a less toxic, hydroxylated version of chloroquine first synthesized in 1946. As an important differentiator from chloroquine, hydroxychloroquine is preferred in regard to its safety profile and minimal risk of retinal toxicity. HCQ was found to be ~40% less toxic than chloroquine according to McChesney et al.

Mechanistically, Both agents have been shown to inhibit viral entry and post-entry activity in vitro. Liu et al. have noted that they elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes. That disruption could inhibit membrane fusion, as could the glycosylation of the ACE2 receptor and spike protein

Product Characteristics

- **Oral Tablet**
- **Prescribed to adults, children and pregnant women**
- **Relatively well tolerated.** Common adverse effects include: stomach pain, nausea, vomiting and headache. The side effects can be lessened if chloroquine is taken with food.
- **Cheap and relatively easy to manufacture.**

Current Status

Chloroquine is currently approved in the U.S. and Is used for the treatment of malaria and chemoprophylaxis. Hydroxychloroquine was first approved in the US in 1955 and is currently indicated for the treatment or prophylaxis of malaria (uncomplicated malaria due to *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*) as well as treatment of rheumatoid arthritis, systemic and discoid lupus erythematosus, and other dermatologic conditions. Of note, hydroxychloroquine (as well as chloroquine) are known to be broad-spectrum antivirals.

As of 3/19/2020, HCQ sulfate tablets were placed on a drug shortage list according to the American Society of Health-System Pharmacists (separate from the FDA).

COVID-19 Status

Based on preclinical and some anecdotal data, both agents are recommended treatments for COVID-19 in several countries. In the US, hydroxychloroquine is the preferred agent given the superior tolerability profile and broader availability. There have been no RCTs to help guide dosing here, thought the CDC notes that typical dosing regimens being utilized in the off-label setting include: 400mg BID on day one, then daily for 5 days; 400 mg BID on day one, then 200mg BID for 4 days; 600 mg BID on day one, then 400mg daily on days 2-5.

Supply: With the potential to use HCQ as a preventative measure or treatment for COVID-19, several generic manufacturers have announced that they will ramp-up manufacturing and supply of the product. Sandoz (Novartis) has committed to donating 130M doses by the end of May, Teva is donating more than 6M doses by the end of March and more than 10M doses within a month, Mylan will provide 50M doses by mid-April, and Amneal plans to produce 20M tablets by mid-April.

Source: Company reports, clinicaltrials.gov, Guggenheim Securities LLC Research

CQ / HCQ - Relevant Preclinical Data Summary

Coronavirus

***In Vitro* SARS-CoV**

- In Vero E6 cells, Keyaerts et. al. demonstrated that chloroquine was an effective inhibitor of replication for SARS-CoV.
- In primate cells, chloroquine showed strong antiviral activities again SARS-CoV both as a prophylactic and a therapeutic intervention. Chloroquine functioned through increasing endosomal pH, and interfering with the glycosylation of cellular receptors, like angiotensin-converting enzyme 2, of SARS-CoV.

***In Vitro* MERS-CoV**

- A high-throughput assay demonstrated that chloroquine inhibits viral replication at low-micromolar concentrations (EC50= 3.0 μM) in Vero and Huh7 cells. In this assay, they also replicated previous results showing chloroquine inhibited viral replication for SARS-CoV and human coronavirus 229E.

***In Vivo* SARS-CoV**

- In a mouse model of SARS-CoV replication, chloroquine was shown to be inactive *in vivo*. One hypothesis was that while chloroquine reduced the hyperinflammatory response, it was unable to prevent replication *in vivo*, the main driver of the inflammatory response. It was suggested that Chloroquine might be effective to reduce disease progression, if given in combination with agents that prevent replication.

COVID-19

***In Vitro* COVID-19**

- In a 2020 Nature letter to the editor, Wang M. et al. demonstrated that chloroquine and remdesivir potently block viral infection of COVID-19 at low-micromolar concentrations (RDV EC50=0.77 uM and chloroquine EC50=1.13 uM) in a time-of-addition assay with Vero E6 cells. Chloroquine worked at both entry, and at post-entry stages of infection to block viral infection.
- The EC_{90} value of chloroquine COVID-19 in Vero E6 cells was 6.90 μM. This is clinically achievable in patients, as shown in the plasma of rheumatoid arthritis patients who received 500 mg of Chloroquine.
- Hydroxychloroquine was shown to be more potent than chloroquine at inhibiting COVID-19 in Vero cells. From pharmacokinetic modeling based on *in vitro* data, a dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days was recommended.

***In Vivo* COVID-19**

- Gao et al. recently published on the use of chloroquine on more than 100 patients with COVID-19 in China. They said that chloroquine was superior to the control treatment in inhibiting pneumonia and shortening the disease course. However, they did not publish the data from the 10 study sites, so it's difficult to come to a conclusion from their statements.
- An Italian group just completed a clinical trial in which they treated COVID-19 positive patients with chloroquine and antibiotic azithromycin. They demonstrated positive results, but the trial had a small sample size, so while promising, larger clinical trials need to be completed.

Source: Guggenheim Securities LLC Research; clinicaltrials.gov

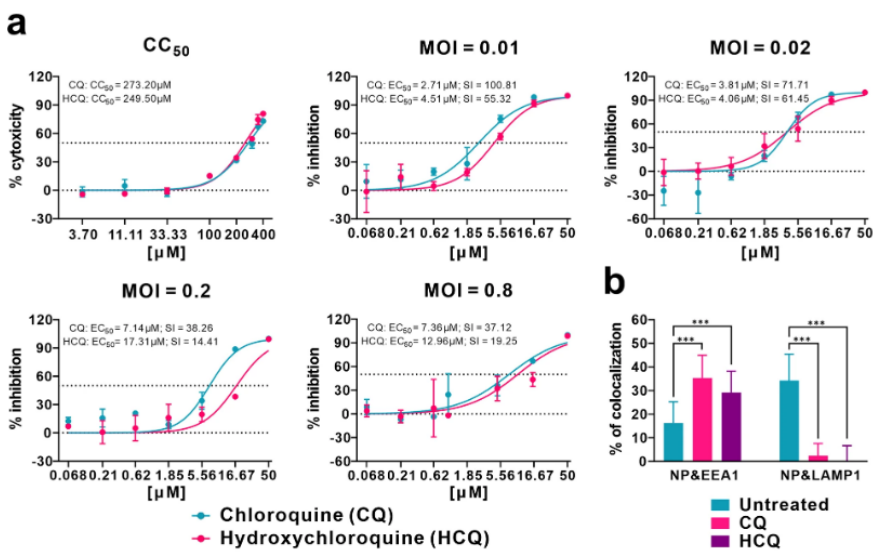
HCQ - Relevant Preclinical Data Summary

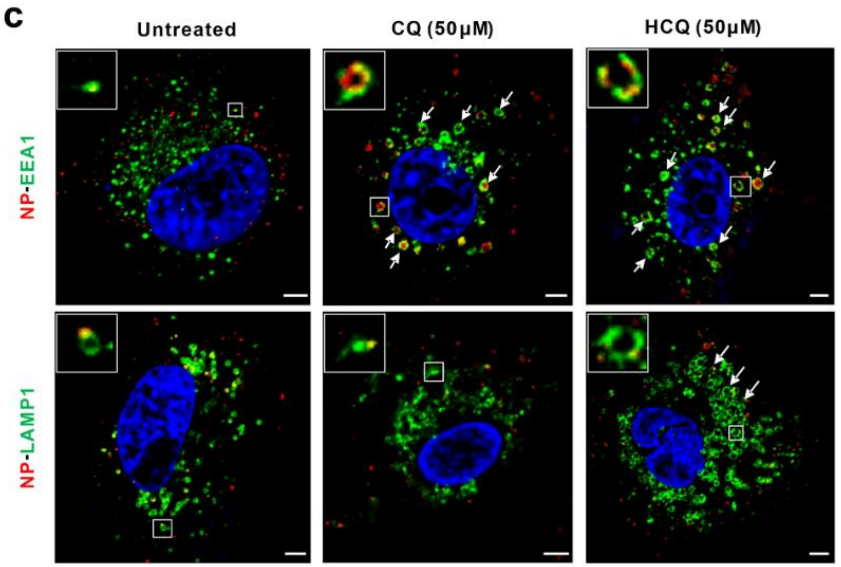
Several clinical studies registered in the Chinese Clinical Trial Registry are using hydroxychloroquine to treat COVID-19. Although no results are yet published, in a letter to the editor, Liu et al. showed that HCQ is effective in inhibiting SARS-CoV-2 infection *in vitro*.

Summary of *in vitro* results:

Exhibit A: This exhibit shows the cytotoxicity of CQ and HCQ treated Vero E6 cells (as determined by CCK-8 assays). The data show at all MOIs (0.01, 0.02, 0.2, and 0.8), the 50% maximal effective concentration (EC_{50}) for CQ (2.71, 3.81, 7.14, and 7.36 μM) was lower than that of HCQ (4.51, 4.06, 17.31, and 12.96 μM). The differences in EC_{50} values were statistically significant at an MOI of 0.01 ($P < 0.05$) and MOI of 0.2 ($P < 0.001$).

Exhibit B & C: These exhibits confirmed that HCQ effectively inhibited the entry step, as well as the post-entry stages of SARS-CoV-2, which was also found upon CQ treatment. **Exhibit C** further explores the mechanism of action of CQ and HCQ in inhibiting virus entry, co-localization of virions with early endosomes (EEs) or endolysosomes (ELs) was analyzed by immunofluorescence analysis (IFA) and confocal microscopy. Quantification analysis showed that, at 90 min p.i. in untreated cells, 16.2% of internalized virions (anti-NP, red) were observed in early endosome antigen 1 (EEA1)-positive EEs (green), while more virions (34.3%) were transported into the late endosomal–lysosomal protein LAMP1$^+$ ELs (green). In contrast, when treated with CQ or HCQ, significantly more virions (35.3% for CQ and 29.2% for HCQ; $P < 0.001$) were detected in the EEs, while only very few virions (2.4% for CQ and 0.03% for HCQ; $P < 0.001$) were found to be co-localized with LAMP1$^+$ Els. This suggests that both CQ and HCQ blocked the transport of SARS-CoV-2 from EEs to ELs, which appears to be a requirement to release the viral genome for SARS-CoV.





Source: Guggenheim Securities, LLC; Liu et al.

HCQ - Relevant Clinical Data Summary

Based on an abstract (no published clinical results) chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2 in Chinese COV-19 patients.

Recently, a French group led by Didier Raoult has completed and published on a successful trial.

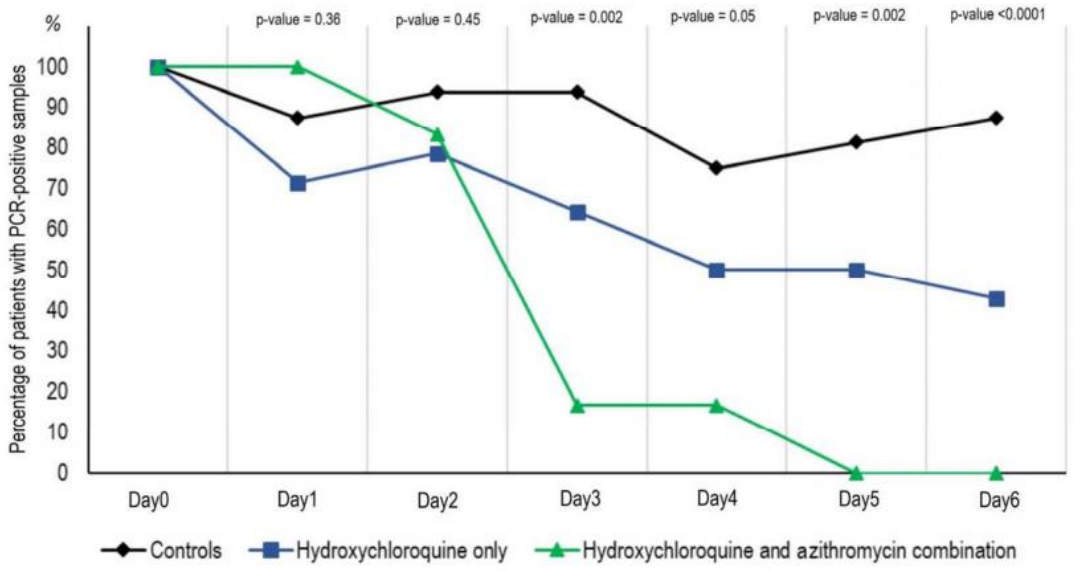
Enrollment:	30
Design:	Open-Label, Nonrandomized
Study Start Date:	Early March 2020
Estimated Primary Completion:	March 16, 2020
Treatment:	1. 600mg of HCQ daily 2. 600mg of HCQ daily and antibiotic azithromycin 3. Control - No treatment
Primary Endpoint:	Incidence presence and absence of viral load Day 6 post inclusion in nasopharyngeal swabs

All of the 30 patients were COVID-19 positive: 6 patients were asymptomatic, 22 had upper respiratory tract infection and 8 had lower respiratory tract infections. The 20 patients that were treated in the study showed a significant reduction in viral load 6 days post inclusion compared to controls and a shorter carriage duration compared to untreated patients in the literature. Once Azithromycin was added into the treatment regimen, hydroxychloroquine was much more efficient at eliminating the virus.

In summary, the trial showed that hydroxychloroquine alone, or in combination with Azithromycin is effective at eliminating COVID-19 compared to controls.

While the data was promising, the sample size for the clinical trial was very small, N=30, and the study does not assess clinical benefit. Larger trials are necessary to confirm the antiviral activity of HCQ and azithromycin against COVID-19.

Clinical Trial Data



Source: Guggenheim Securities, LLC; Gautret et al.

CQ / HCQ - Ongoing Clinical Trials (Global)

Chloroquine is currently being evaluated in 23 trials globally. The WHO is also launching a multi-country SOLIDARITY trial with Chloroquine as one of 4 drugs tested.

NCT ID / trial link	Title	Enrollment	Sponsor	Geography	Primary Est. Completion
NCT04303507	Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting; a Randomised, Placebo-controlled Prophylaxis Study (COPCOV)	N=10,000	University of Oxford	U.K.	05/2022
NCT04308668	Post-exposure Prophylaxis for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial	N = 1500	University of Minnesota	Minnesota, U.S.	May 2021
NCT04304053	Antiviral Treatment of COVID-19 Confirmed Cases and Ring Chloroquine Chemoprevention in Close Contacts: a Cluster Randomized Clinical Trial	N=3,040	Lihir Medical Centre		07/15/2020
NCT04286503	The Efficacy and Safety of Carrimycin Treatment in Patients With Novel Coronavirus Infectious Disease (COVID-19) : A Multicenter, Randomized, Open-controlled Study	N=520	Beijing YouAn Hospital	China	02/28/2021
NCT04303299	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19 : A Randomized Control Trial (THDMS-COVID19)	N=80	Rajavithi Hospital	Thailand	10/31/2020
NCT04306497	Clinical Trial on Regularity of TCM Syndrome and Differentiation Treatment of COVID-19 in Jiangsu Province	N=340	Jiangsu Famous Medical Tech Co	China	05/2020
	WHO SOLIDARITY Trial				
NCT04315896	Hydroxychloroquine Treatment for Severe COVID-19 Pulmonary Infection (HYDRA Trial)	N=500	NIRD, Mexico	Mexico	10/31/2020
NCT04316377	Norwegian Coronavirus Disease 2019 Study: An Open Labeled Randomized Controlled Pragmatic Trial to Evaluate the Antiviral Effect of Chloroquine in Adult Patients With SARS-CoV-2 Infection	N=202	University Hospital, Akershus	Norway	04/01/2021
NCT04261517	Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)	N=30	Shanghai Public Health Clinical Center	China	8/31/2020
NCT04307693	Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	N=150	Asan Medical Center	Korea	05/2020

Source: Clinicaltrials.gov; ChiCTR

CQ / HCQ - Ongoing Clinical Trials (China) - 1

Chinese Clinical Trial Registration/ trial link	Title	Enrollment	Sponsor	Primary Est. Completion
ChiCTR2000029939	A Single-blind, Randomized, Controlled Clinical Trial for Chloroquine Phosphate in the treatment of Novel Coronavirus Pneumonia 2019 (COVID-19)	N=100	HwaMei Hospital, University of Chinese Academy of Sciences	02/06/2021
ChiCTR2000029935	A Single-arm Clinical Trial for Chloroquine Phosphate in the treatment of Novel Coronavirus Pneumonia 2019 (COVID-19)	N=100	HwaMei Hospital, University of Chinese Academy of Sciences	02/06/2021
ChiCTR2000029899	Evaluation the Efficacy and Safety of Hydroxychloroquine Sulfate in Comparison with Phosphate Chloroquine in Mild and Commen Patients with Novel Coronavirus Pneumonia (COVID-19): a Randomized, Open-label, Parallel, Controlled Trial	N=100	Peking University Third Hospital	04/30/20
ChiCTR2000029898	Evaluation the Efficacy and Safety of Hydroxychloroquine Sulfate in Comparison with Phosphate Chloroquine in Severe Patients with Novel Coronavirus Pneumonia (COVID-19): a Randomized, Open-Label, Parallel, Controlled Trial	N=100	Peking University Third Hospital	04/30/20
ChiCTR2000029868	Hydroxychloroquine treating novel coronavirus pneumonia (COVID-19): a multicenter, randomized controlled trial	N=200	Ruijin Hospital, Shanghai Jiaotong University School of Medicine	07/31/2020
ChiCTR2000029837	Cancelled by the investigator A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in mild/common patients with novel coronavirus pneumonia (COVID-19)	N=120	Jingzhou Central Hospital	03/17/2020
ChiCTR2000029826	Cancelled by the investigator A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in serious/critically ill patients with novel coronavirus pneumonia (COVID-19)	N=45	Jingzhou Central Hospital	03/17/2020

Source: Clinicaltrials.gov; ChiCTR

CQ / HCQ - Ongoing Clinical Trials (China) - 2

Chinese Clinical Trial Registration/ trial link	Title	Enrollment	Sponsor	Primary Est. Completion
ChiCTR2000029803	A prospective, randomized, open-label, controlled clinical study to evaluate the preventive effect of hydroxychloroquine on close contacts after exposure to the Novel Coronavirus Pneumonia (COVID-19)	N=320	Renmin Hospital of Wuhan University	02/20/2021
ChiCTR2000029762	Cancelled due to lack of patient A randomized, open-label, controlled trial for the efficacy and safety of hydroxychloroquine sulfate tablets in the treatment of patients with severe novel coronavirus pneumonia (COVID-19)	N=60	The First Affiliated Hospital of Chongqing Medical University	
ChiCTR2000029761	Cancelled due to lack of patient Clinical study on the safety and effectiveness of Hydroxychloroquine Sulfate tablets in the treatment of patients with novel coronavirus pneumonia (COVID-19)	N=240	The First Affiliated Hospital of Chongqing Medical University	04/30/2020
ChiCTR2000029760	Cancelled due to lack of patient A study for the efficacy of hydroxychloroquine for mild and moderate COVID-19 infectious diseases	N=240	The Second Affiliated Hospital of Chongqing Medical University	08/22/2020
ChiCTR2000029741	Efficacy of Chloroquine and Lopinavir/ Ritonavir in mild/general novel coronavirus (CoVID-19) infections: a prospective, open-label, multicenter randomized controlled clinical study	N=112	The Fifth Affiliated Hospital Sun Yat-Sen University	12/31/2020
ChiCTR2000029740	Efficacy of therapeutic effects of hydroxycholoroquine in novel coronavirus pneumonia (COVID-19) patients（randomized open-label control clinical trial）	N=78	The First Hospital of Peking University	02/29/2020
ChiCTR2000029609	A prospective, open-label, multiple-center study for the efficacy of chloroquine phosphate in patients with novel coronavirus pneumonia (COVID-19)	N=205	The Fifth Affiliated Hospital of Sun Yat-Sen University	12/31/2020
ChiCTR2000029559	Therapeutic effect of hydroxychloroquine on novel coronavirus pneumonia (COVID-19)	N=300	Renmin Hospital of Wuhan University	02/29/2020
ChiCTR2000029542	Study for the efficacy of chloroquine in patients with novel coronavirus pneumonia (COVID-19)	N=20	Sun Yat sen Memorial Hospital of Sun Yat sen University	07/20/20

Source: Clinicaltrials.gov; ChiCTR

CQ / HCQ - Ongoing Clinical Trials (China) - 3

Chinese Clinical Trial Registration/ trial link	Title	Enrollment	Sponsor	Primary Est. Completion
ChiCTR2000030987	Clinical Trial of Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of novel coronavirus pneumonia (COVID-19)	N = 150	Beijing Chao-yang Hospital, Capital Medical University	06/25/2020
ChiCTR2000030718	Clinical Study of Chloroquine Phosphate in the Treatment of 2019-nCoV Infection	N = 80	Zhongnan Hospital of Wuhan University	05/30/2020
ChiCTR2000030417	Cancelled by the investigator Efficacy and safety of chloroquine phosphate inhalation combined with standard therapy in the treatment of novel coronavirus pneumonia (COVID-19)	N = 30	Harbin infectious diseases hospital	06/30/2020
ChiCTR2000030054	An open randomized controlled trial for Chloroquine phosphate and Hydroxychloroquine sulfate in the treatment of mild and common novel coronavirus pneumonia (COVID-19)	N = 100	Zhongshan Hospital Affiliated to Xiamen University	05/21/2020
ChiCTR2000030031	Cancelled by the investigator A randomized, double-blind, parallel, controlled trial for comparison of phosphoric chloroquine combined with standard therapy and standard therapy in mild/common patients with novel coronavirus pneumonia (COV	N = 120	The Sixth Affiliated Hospital of Guangzhou Medical University (Qingyuan People's Hospital)	03/20/2021
ChiCTR2000029992	An open randomized controlled trial for Chloroquine phosphate and Hydroxychloroquine sulfate in the treatment of severe novel coronavirus pneumonia (COVID-19)	N = 100	Zhongshan Hospital Affiliated to Xiamen University	05/20/2020
ChiCTR2000029988	Clinical Study of Chloroquine Phosphate in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	N = 80	Zhongnan Hospital of Wuhan University	05/31/2020
ChiCTR2000029975	Single arm study for exploration of chloroquine phosphate aerosol inhalation in the treatment of novel coronavirus pneumonia (COVID-19)	N = 10	The First Hospital of Jilin University	05/31/2020

Source: Clinicaltrials.gov; ChiCTR

Remdesivir (RDV) – GILD

Background and Mechanism

Remdesivir is a phosphoramidate prodrug of a 1′-cyano-substitued adenosine analogue. Like other nucleotide analogs, remdesivir works by inhibiting viral replication. Based on work with the Ebola virus, the drug has been to shown to exert its effect through delayed chain termination. More specifically, incorporation of the RDV at position i causes delayed chain termination predominantly at position i+3-5.

It was originally developed for the treatment of Ebola (an enveloped, non-segmented, negative-stranded RNA virus) where the drug showed potent in vitro activity though limited clinical impact in an RCT. Outside of Ebola, the drug has shown broad spectrum antiviral activity against several RNA viruses including SARS-CoV and MERS-CoV.

Current Status / Commentary

Currently remdesivir is not approved anywhere for any use.

Product Characteristics

- **I.V. infusion**
- **Limited available clinical supplies.** Gilead is working to working to increase available supply as rapidly as possible through external and internal manufacturing facilities.
- **There are two formulations: liquid and freeze-dried.**

COVID-19 Status

Remdesivir is being evaluated in 9 clinical trials globally.

Gilead has initiated 2 clinical trials worldwide and has been working with global health authorities (FDA, CDC, DHHS, DoD, NMPA, WHO) and private individuals to respond to the COVID-19 pandemic appropriately with the investigational drug.

Due to lack of treatment measures, remdesivir has been given to patients for emergency treatment under Compassionate Use guidelines. But, the results from these patients is not sufficient to determine the efficacy and safety of remdesivir; only a clinical trial is adequate.

Source: Guggenheim Securities LLC Research; clinicaltrials.gov

RDV – Relevant Data Summary

Ebola

Preclinical

- Preclinically RDV has been shown to potently inhibit several types of filovirus with low levels of cytotoxicity (EC50 = 0.01 to 0.20 µM; CC50 = 2 to >20 µM).
- In a rhesus monkey model of Ebola, Warren et al. showed that QD IV doses of 10 mg/kg for 12 days led to consistent levels of the active form (10 µM) in the blood. RDV treatment suppressed viral replication and conferred 100% protection against lethal disease.

Clinical

- In a large randomized controlled clinical trial (results here) for the treatment of Ebola infection, the RDV dosing regimen was as follows: a loading dose (150mg for pts weighing ≥40 kg and 3.75 mg/kg for pts below that cut off) with subsequent maintenance dosing on days 2 to 10 (100mg for patients ≥40 kg or 2.5mg/kg for <40kg).
- Treatment with RDV did appear to decrease viral load over time, though it proved inferior to other regimens on that measure as well as in decreasing the mortality rate (~53% mortality rate in the RDV arm vs. 33-35% in other arms).
- That said, study authors note several factors that could have impacted RDV efficacy in the study, including that 97% of deaths in the trial occurred within 10 days after enrollment, which puts RDV at an advantage given the need for ongoing dosing (as opposed to one bolus dose).
- Importantly, RDV appeared to be safe and relatively well tolerated in this trial, in line with prior Ph1 and compassionate use experience.
- In vitro, different inhibition patterns of Ebola virus RdRp as compared to coronavirus (MERS-CoV) indicates different mechanisms of action.

Coronavirus

***In Vitro* SARS-CoV and MERS-CoV**

- In primary human cell culture (HAE) experiment RDV was shown to have broad spectrum activity against Bat-CoVs, prepandemic Bat-CoVs, and circulating contemporary human-CoV in primary human lung cells.

***In Vivo* MERS-CoV**

- In a murine model of MERS infection, RDV has been shown to reduce lung viral loads, improve pulmonary function and reduce severe lung disease.
- In a 2020 study in rhesus macaques, animals were randomly assigned to one of three groups (n=6 per group): control group (vehicle treated pre or post inoculation), prophylactic (5mg/kg RDV 24 before inoculation) and therapeutic (5gm/kg RDV 12h after inoculation). Animals were dosed QD for 6 days.
- Prophylactic RDV prevented clinical disease and lung lesions in this study, and inhibited viral replication in respiratory tissues.
- Therapeutic RDV reduced the severity of clinical disease (reduced both the rate and severity of lung disease) and viral replication. Study authors note that prevention of lung lesions (as happened in 2 of the 6 therapeutically treated animals) has rarely been observed in NHP studies of other antivirals for MERS treatment.

***In Vitro* COVID-19**

- Another 2020 study that ran a screen of 7 anti-viral agents against the novel COVID-19 strain showed remdesivir and chloroquine to be the most potent inhibitors of infection at lower-molecular concentrations (RDV EC50=0.77 uM and chloroquine EC50=1.13 uM).

Source: Clinicaltrials.gov; ChiCTR

RDV – Ongoing Clinical Trial Summary

NCT ID / trial link	Title	Enrollment	Sponsor	Geography	Primary Est. Completion
NCT04257656	A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Severe 2019-nCoVRespiratory Disease.	N = 453	Capital Medical University	China	4/3/2020
NCT04252664	A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Efficacy and Safety of Remdesivir in Hospitalized Adult Patients With Mild and Moderate 2019-nCoV Respiratory Disease.	N = 308	Capital Medical University	China	04/10/2020
NCT04302766	Intermediate-Size Patient Population Expanded Access Treatment Protocol for Coronavirus Disease 2019 (COVID-19) Remdesivir (RDV; GS-5734™)		U.S. Army Medical Research and Development Command		
NCT04292899	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe COVID-19	N = 400	Gilead Sciences		May 2020
NCT04292730	A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Compared to Standard of Care Treatment	N = 600	Gilead Sciences		May 2020
NCT04280705	A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults	N = 394	National Institute of Allergy and Infectious Diseases (NIAID)		04/01/2023
NCT04315948	Multi-centre, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults	N = 3200	Institut National de la Santé Et de la Recherche Médicale, France	France	March 2023
NCT04314817	Adverse Events Related to Treatments Used Against Coronavirus Disease 2019	N = 1000	Groupe Hospitalier Pitie-Salpetriere	France	01/01/2021
	WHO SOLIDARITY Trial				

Source: Clinicaltrials.gov; ChiCTR

Favipiravir (FPV) – Fujifilm

Background and Mechanism

Favipiravir (FPV) is a RNA polymerase inhibitor approved for influenza in Japan. Favipiravir works similar to other nucleoside analogs by inhibiting viral replication by inhibiting RNA-dependent RNA polymerase (RdRp). As a reminder, most therapies aim to inhibit one of the following points of the virus lifecycle: viral entry into the host cell, viral replication, and viral RNA synthesis. Favipiravir is phosphoribosylated to its active form where it is recognized as a purine nucleotide by RdRp, blocking synthesis and replication.

Favipiravir was originally developed by Fujifilm for influenza. It has also demonstrated efficacy in a variety of other viruses, including Ebola. Following approval for clinical testing established in February, initial study results from two trials from Shenzhen and Wuhan have been published.

Product Characteristics

- **Oral tablet**
- **Safety – teratogenicity and embryotoxicity.** Favipiravir is contraindicated in pregnant and lactating women by the Japanese Ministry of Health.
- **Potentially best suited prior to severe disease in asymptomatic, mild, or moderate patients.** RdRp inhibitors prevent the virus from proliferating, though not protecting against other factors beyond the virus such as the damage induced by the body's own immune response

Current Status / Commentary

Currently favipiravir is marketed by Fujifilm in Japan as Avigan and by Zhejiang Hisun Pharmaceuticals in China as Favilavir

COVID-19 Status

Favipiravir is currently being evaluated in numerous clinical trials globally.

The drug was approved to be tested in clinical trial in China for COVID-19 on February 17th. On March 17th, China Daily and the Guardian reported that Zhang Xinmin, head of the China National Center for Biotechnology Development, stated that clinical study results from two trials of favipiravir were encouraging. Results from the Third People's Hospital of Shenzhen study and Zhongnan Hospital of Wuhan University study have been published.

In addition to monotherapy, favipiravir is being evaluated in combination with other regimens.

Source: Guggenheim Securities LLC Research; clinicaltrials.gov

FPV – Ongoing Clinical Trials – 1

Favipiravir (T-705 / Avigan / Favilavir) is currently being evaluated in multiple trials globally, and is additionally included as a potential treatment in the control arm of another study assessing bromhexine hydrochloride in China.

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04310228 ChiCTR2000030894	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019	150	Peking University First Hospital	China	05/2020
NCT04303299	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19 : A Randomized Control Trial	80	Rajavithi Hospital	Thailand	10/2020
ChiCTR2000030987	A Randomized Controlled Trial for Favipiravir Tablets Combine With Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia (COVID-19)	150	Beijing Chao-yang Hospital, Capital Medical University	China	6/25/2020
ChiCTR2000030113	Randomized controlled trial for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19) with poorly responsive ritonavir/ritonavir	30	The Third People's Hospital of Shenzhen	China	5/31/2020
ChiCTR2000029600	Clinical study for safety and efficacy of Favipiravir in the treatment of novel coronavirus pneumonia (COVID-19)	90	The Third People's Hospital of Shenzhen	China	Reported
ChiCTR2000029548	Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients	30	The First Affiliated Hospital, Zhejiang University School of Medicine	China	6/3/2020
ChiCTR200030254	Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial	236	Zhongnan Hospital of Wuhan University	China	Reported
ChiCTR2000029544	A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy	30	The First Hospital Affiliated to Zhejiang University's Medical School	China	5/31/2020

Source: Clinicaltrials.gov; ChiCTR

FPV – Ongoing Clinical Trials – 2

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
ChiCTR2000029996	A randomized, open-label, controlled trial for the efficacy and safety of Farpiravir Tablets in the treatment of patients with novel coronavirus pneumonia (COVID-19)	60	Beijing Chaoyang Hospital, Capital Medical University	China	4/20/2020
jRCTs031190226	Favipiravir in patients infected with COVID-19	50	Gunma University Hospital	Japan	-
jRCTs041190120	Favipiravir for SARS-CoV-infected patients	86	Japan Agency for Medical Research and Development	Japan	-

Source: NIPH Clinical Trials Search, Clinicaltrials.gov; ChiCTR

FPV – Relevant Data Summary

In Vitro COVID-19 data

- A 2020 study that ran a screen of 7 anti-viral agents against the novel COVID-19 strain. High concentrations of favipiravir were required to reduce viral infection (EC50 = 61.88 μM, CC50 > 400 μM, SI > 6.46) compared to remdesivir and chloroquine (RDV EC50=0.77 uM and chloroquine EC50=1.13 uM).
- The authors do note that in Ebola, favipiravir was 100% effective in protecting mice against Ebola virus although its EC50 value in Vero E6 cells was as high as 67 μM.

Initial clinical results

On March 17th, China Daily and the Guardian reported that Zhang Xinmin, head of the China National Center for Biotechnology Development, stated that clinical study results from two trials of favipiravir were encouraging.

- The Third People's Hospital of Shenzhen study (ChiCTR2000029600) – this open-label non-randomized study in 80 patients (non-severe) evaluated FPV + interferon (IFN)-α inhalation (n=35), with LPV/RTV + IFN-α inhalation treated as control (n=45). Patients received FPV doses for 14 days (Day 1: 1,600 mg twice daily; Days 2–14: 600 mg twice daily). Results showed a shorter time to viral clearance in the FPV arm with a median time to recovery of 4 days vs 11 days for control, as well as significant improvement in chest imaging measured by CT, with an improvement rate of 91.43% versus 62.22% (P = 0.004). With Safety, AEs in the FPV arm were significantly lower than in the control arm
- Zhongnan Hospital of Wuhan University (ChiCTR200030254) – this open-label, randomized superiority study in 240 moderate COVID-19 patients evaluated FPV (n=116) to Arbidol (n=120). Patients received FPV doses for 7-10 days (Day 1: 1,600 mg twice daily; Days 2-7/10: 600 mg twice daily) Results from the 236 patients showed more rapid improvement in the FPV group (including fevers, cough, respiratory frequency, oxygen), with 7 day's clinical recovery rate of 71.43% vs. 55.86% in the arbidol group (p = 0.0199). However, there was no statistical difference was observed of auxiliary oxygen therapy or noninvasive mechanical ventilation rate (both P > 0.05). Both groups performed poorly in critical patients, with 0 patients in the Arbidol group and 1/18 patients in the FPV group considered clinically recovered. The most common AE was raised levels of serum uric acid, which was more common in the FPV group (14%).

There are also trials ongoing in Japan, and a Japanese health ministry source (per the Guardian) suggested that favipiravir was not as effective in patients with more severe symptoms.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

Prezista (Darunavir / DRV) and Prezcobix (Darunavir / Cobicistat) - JNJ

Background and Mechanism

Prezista is a human immunodeficiency virus (HIV-1) protease inhibitor indicated for the treatment of HIV-1 infection in adult and pediatric patients 3 years of age and older. It must be co-administered with a pharmacokinetic booster (e.g. ritonavir, cobicistat) and with other antiretroviral agents.

Darunavir selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles. It was initially approved in 2006, and the fixed-dose combination with cobi (Prezcobix) was approved in 2015.

Product Characteristics

- **Oral Tablet and oral suspension**
- **Approved in the US**
- **Relatively well tolerated.** Common adverse effects with at least moderate intensity include: diarrhea, nausea, rash, headache, abdominal pain and vomiting. Should be taken with food.
- **Treatment-naïve and treatment-experienced adult patients with no darunavir resistance associated substitutions should take one 800 mg tablet with ritonavir 100 mg once daily and with food.**

COVID-19 Status

JNJ had announced through a press release that there is a lack of evidence to support the use of darunavir for COVID-19 (see below).

Many Janssen compounds, including darunavir, are in the process of being evaluated in-vitro for potential antiviral activity against SARS-CoV-2. Janssen has also provided DVR-based medicines to support three clinical studies in China. As soon as these data become available, we will update this information.

There are no published studies with darunavir in any coronavirus (including SARS or MERS)-related disease, including in vitro studies. In addition to JNJ's information on the product provided below, this is unlikely to be a treatment for COVID-19.

From a JNJ press release on March 17th, 2020:

"… Janssen has no clinical nor pharmacological evidence to support the inclusion of DRV/cobicistat in treatment guidelines for COVID-19, nor are there published data on the safety and efficacy profile of DRV/cobicistat in treatment of COVID-19.

In addition, there are no published in-vitro studies with DRV and coronavirus. Based on preliminary, unpublished results from a previously reported in-vitro experiment, it is not likely DRV will have significant activity against SARS-CoV-2 when administered at the approved safe and efficacious dose for the treatment of HIV-1 infection.

Additionally, structural analyses show very few interactions of DRV with the active site of the SARS-CoV-2 protease…"

Sources: UpToDate; AdisInsight; Package Insert; JNJ Press Release

DRV – Ongoing Clinical Trials (Global)

Prezista (darunavir) is currently being evaluated in 1 trial in Thailand that is assessing a whole host of antiviral therapies such as the below on their effectiveness in SARS-CoV-2 eradication time (up to Week 24), which is defined as the eradication of nasopharyngeal SARS-CoV-2.

1. Oseltamivir + Chloroquine
2. Lopinavir/Ritonavir + Favipiravir
3. Lopinavir/Ritonavir + Oseltamivir
4. Darunavir/Ritonavir + Oseltamivir + Chloroquine
5. Darunavir/Ritonavir + Favipiravir + Chloroquine

Prezcobix (Darunavir / Cobicistat) is currently being evaluated in 2 trials; the first one is a randomized clinical trial with parallel assignment across two treatment arms (vs. conventional treatments that exclude darunavir and cobicistat. The trial is assessing treatment effect on the virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 7.

The second trial assesses Prezcobix (darunavir 800 mg / cobicistat 150 mg) tablets (1 tablet taken QD, for 7 days) in combination with hydroxychloroquine (200mg) tablets (800mg taken on day 1 and 400mg on days 2, 3, and 4) against a comparator arm with no intervention and SARS-CoV-2 surveillance.

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04303299 THDMS-COVID19	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19: A Randomized Control Trial	80	Rajavithi Hospital	Thailand	10/2020
NCT04252274D ACO-nCoV	Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV	30	Shanghai Public Health Clinical Center	China	08/2020
NCT04304053 HCQ4COV19	Treatment of Mild Cases and Chemoprophylaxis of Contacts as Prevention of the COVID-19 Epidemic	3040	Lihir Medical Centre / Laboratorios Gebro Pharma SA / Laboratorios Rubió SA	Spain	07/2020

Source: Clinicaltrials.gov; ChiCTR

Umifenovir (Arbidol hydrochloride / Abidol HCl / Abidole)

Background and Mechanism

Umifenovir (arbidol hydrochloride) is an indole-derivative antiviral, specifically a membrane fusion inhibitor. It is made by Moscow-based Pharmstandard and has been shown to be an entry inhibitor against influenza; it is used outside the United States as a treatment for influenza. It has also shown potent activity against HHV-8 in vitro. However, there have been no clinical studies conducted with it and its mechanism of action remains unclear.

Umifenovir has been researched since the 1990s in respiratory diseases. Its activity as a membrane fusion inhibitor is thought to have an immunomodulating and anti-influenza effect (specifically against influenza groups A and B, and SARS). By inhibiting fusion of viral lipid membranes with those of the cell membrane, it prevents contact and entry of the virus into cells. Additionally, it has an interferon-inducing action, which stimulates immunity (humoral and cell-mediated), helping phagocytosis by macrophages.

Product Characteristics

- **Oral Tablet**
- Not approved (in the US), but has been used in Russia and China for adult and pediatric influenza patients
- **Relatively well tolerated.** Common adverse effects include: allergic rash and advised to take on an empty stomach.
- Maximum plasma concentration is achieved quickly (within ~1 hour) and has a $t_{1/2}$ of ~20 hours. It is metabolized by the liver and thus should be avoided with CYP inhibitors (e.g., macrolide antibiotics, statins)
- Presumably cheap and relatively easy to manufacture.

Current Status

Arbidol is currently used for treating influenza in Russia and China.

The antiviral product Arpetol (umifenovir) has been listed on the WHO's recommended medicines list since 2013.

Additionally, it is included as one of the antivirals within in the 6th edition of the Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia issued by the National Health Commission (NHC) of the People's Republic of China for tentative treatment of COVID-19.

COVID-19 Status

China's Changjiang Daily first reported on the drug's potential to inhibit the virus as a team of researchers at Zhejiang University were researching the drug along with darunavir, while the National Health Commission commented that the drug was effective in curbing COVID-19.

Jieming QU along with others have seen arbidol effectiveness against a variety of coronaviruses in vitro pharmacodynamics (in the absence of 2019-nCoV specific therapeutic drugs); NCT04260594

The Chinese State Council's Novel Coronavirus Pneumonia Epidemic Joint Prevention and Joint Control Mechanism Medical Materials Safeguard Team (Materials Safeguard Team) ordered 50,000 boxes of the drug (12 capsules per box) on 2/19/2020 for delivery to the Hubei province by 2/26/2020.

There are a number of ongoing trials assessing its use, but a retrospective case series by Wang Z gives insights into its effectiveness as no patients in the active arm died (vs. 5 in the control arm; n=69)

It also included in the control arm for (1) a trial assessing thalidomide, along with α-interferon and methylprednisolone, (2) another trial assessing bromhexine, along with Interferon α2b spray, (3) a trial assessing traditional Chinese medicine, and (4) a trial assessing carrimycin).

Sources: UpToDate; AdisInsight; Harrison C, Nature Biotechnology 2020.; Dong L, Hu S, Gao J. Drug Discov Ther. 2020;14(1):58-60.; Belarus Pharmaceuticals Lekpharm Profile

Umifenovir – Relevant Clinical Data Summary

Wang Z. et al

In a placebo controlled study in China, N=67 hospitalized patients were assessed retrospectively (Jan 2020). Many experienced fever (87%) and cough (55%). Patients were segmented by SpO2 (≥90% group had n=55 and <90% had n=14; which had all 5 deaths). Given arbidol's use in China, the MOA of inhibiting virus-mediated fusion with target membrane and thus blocking entry of the virus into cells, arbidol was used. It showed tendency to improve discharging rate and reduce mortality; however, sample size was limited here and a randomized controlled trial is required to assess its efficacy and safety in patients infected with SARS-CoV-2.

Table 5: Outcomes of COVID-19 patients treated with arbidol.

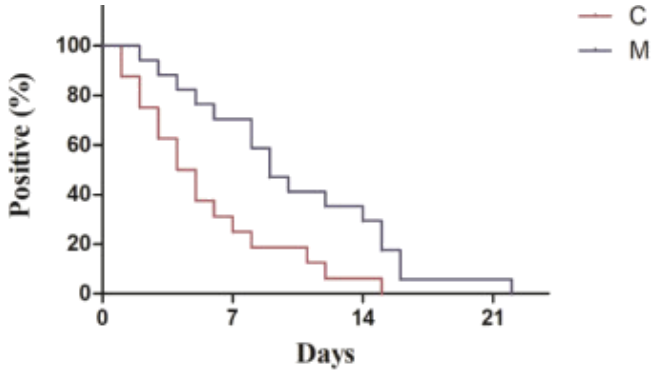
Prognosis	Arbidol-treated group (n=36)	Arbidol-untreated group (n=31)	p value
Hospitalization	24(67%)	20(65%)	0.03
Discharge	12(33%)	6(19%)	..
Death	0	5(16%)	..

Deng L. et al

In a retrospective cohort study comparing arbidol and lopinavir/ritonavir(LPV/r) (C) against LPV/r only (M), 56 patients were evaluated and 33 included in the analysis. All of the 33 patients were COVID-19 positive with n=5/16 (active) and n=6/17 (control) patients with a high (4/4) overall lung "total severity score". After treatment for 7 days, 12 (75%) of 16 patients' nasopharyngeal specimens were negative for SARS-CoV-2's test by RT-PCR in the active group vs. 6 (35%) of 17 in the monotherapy group ($p < 0{\cdot}05$). After 14 days, 15 (94%) of 16 and 9 (53%) of 17, respectively, coronavirus could not be detected ($p < 0{\cdot}05$). Chest CT scans were improving for 11 (69%) of 16 patients in the combination group after 7 days, compared with 5 (29%) of 17 in the monotherapy group ($p < 0{\cdot}05$).

In summary, the trial showed that arbidol in combination demonstrates a higher efficacy than lopinavir/ritonavir alone. The sample size was very small and the study was retrospective in design. Larger studies are ongoing.

Study Start Date:	January 17, 2020 (last diagnosed on February 13, 2020)
Estimated Primary Completion:	March 2020
Treatment:	1. Arbidol (200mg Q 8 h) + lopinavir (400 mg)/ritonavir (100 mg) orally Q 12 h for 5-21 days (n=16) 2. Lopinavir (400 mg)/ritonavir (100 mg) orally Q 12 h for 5-21 days (n=17)
Primary Endpoint:	Negative conversion rate of SARS-CoV-2 from the date of COVID-19 diagnosis (day 7, day 14), and whether pneumonia was progressing or improving by chest CT (day 7).



Source: Beigel JH et al., Antiviral Res. 2019 Jul;167:45-67.; Drug Discoveries & Therapeutics. 2020; 14(1):58-60; J Infect. 2020 Mar 11. pii: S0163-4453(20)30113-4.; Clin Infect Dis. 2020 Mar 16. pii: ciaa272.

Umifenovir – Ongoing Clinical Trials (Global)

Umifenovir (arbidol HCl) is currently being evaluated in 4 trials in China and is additionally included as a potential treatment of part of the treatment in the control arms of four other studies being conducted in China.

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04255017	An Open, Prospective/Retrospective, Randomized Controlled Cohort Study to Compare the Efficacy of Three Antiviral Drugs (Abidol Hydrochloride, Oseltamivir and Lopinavir/Ritonavir) in the Treatment of 2019-nCoV Pneumonia	400	Tongji Hospital	China	06/2020
NCT04254874	An Open, Prospective/Retrospective, Randomized Controlled Cohort Study to Compare the Efficacy of Two Therapeutic Schemes (Abidol Hydrochloride, Abidol Hydrochloride Combined With Interferon Atomization) in the Treatment of 2019-nCoV Pneumonia.	100	Tongji Hospital	China	06/2020
NCT04260594	Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus	380	Ruijin Hospital	China	07/2020
NCT04252885 ELACOI	The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection	125	Guangzhou 8th People's Hospital	China	05/2020

Source: Clinicaltrials.gov; ChiCTR

Kaletra/Aluvia (Lopinavir/Ritonavir; LPV/r) – ABBV/generic

Background and Mechanism

Kaletra (Lopinavir/Ritonavir; LPV/r) is an antiviral often used with other antiretroviral medicines to treat human immunodeficiency virus-1 (HIV-1) infection in adults and children 14 days of age and older. It was approved in 2000 and is manufactured by ABBV. The drug falls within the HIV-1 protease inhibitor class and the addition of ritonavir in the combination pill allows a greater plasma level concentration of lopinavir to be maintained as it inhibits the CYP3A4 metabolism of the drug.

Lopinavir is a second-generation protease inhibitor (PI) of the HIV-1 virus and is reported to be around 10x more active against HIV *in vitro* vs. ritonavir, but likely greater potential for resistance. Given the position lopinavir binds to its target differs from common resistance on the HIV protease gene, this can be used in patients who have developed resistance to other PIs.

Product Characteristics

- **Oral Tablet (Aluvia); oral capsule (Kaletra)**
- **Approved in the US for treating HIV-1 infection as part of combination therapy**
- **Relatively well tolerated.** Common adverse effects include: diarrhea, nausea, vomiting, hypertriglyceridemia and hypercholesterolemia. It can be taken without regard to food
- **Similar to other antivirals, recommended not to be taken with medications that are CYP3A mediators; in this case, inducers (e.g., dexamethasone, carbamazepine, phenytoin, and rifampin)**
- **Generics are available and thus presumably cheap and relatively easy to manufacture.**

COVID-19 Status

The Chinese health authorities have requested (in late January) supply of Aluvia (lopinavir/ritonavir) as part of the government's broader efforts to address the coronavirus crisis in China and thus ABBV has made a donation of Aluvia as an experimental option to support this growing public health crisis. Additionally, ABBV is supporting research of the combination drug with European health authorities, FDA (U.S. Food and Drug Administration), CDC (Centers for Disease Control and Prevention), NIH (National Institutes of Health), and BARDA (Biomedical Advanced Research and Development Authority).

ABBV does not expect a shortage in supply of the drug to HIV patients as a result of this and are continuing to monitor ongoing manufacturing and supply chain as a result of the virus; they do not anticipate supply disruptions.

There was a trial failure in China assessing the therapy for severe COVID-19. (Additionally, a test of ~200 Chinese patients found that that those receiving the treatment had no better outcome than those who received standard of care; details published in the New England Journal of Medicine).

Lopinavir is an HIV protease inhibitor that has been reported to have activity against SARS-CoV-2. It is unclear whether inhibitors of HIV protease (in the aspartic protease family) can effectively inhibit that of 2019-nCoV (in the cysteine protease family), but use for COVID-19 is based largely on trials in severe acute respiratory syndrome (SARS) suggesting that lopinavir was associated with improved clinical outcomes and mortality.

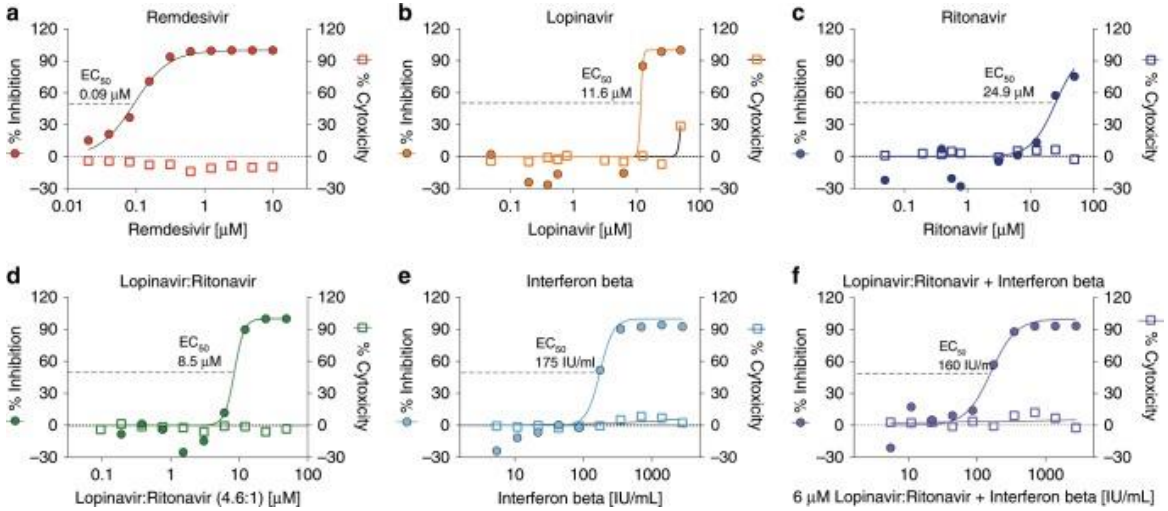
Sources: UpToDate; AdisInsight; ABBV Press Release and Filings (8-k); Package Insert

Kaletra/Aluvia – Relevant Preclinical / Clinical Data Summary

In Vitro

In vitro parallel antiviral activity assays in Calu-3 cells with recombinant MERS-CoV engineered to express a reporter nanoluciferase compared anti-viral activity to other agents.

Remdesivir showed potent inhibition of MERS-CoV replication with a EC50 of 0.09 µM and no observable cytotoxicity up to 10 µM and was highly selective. While compared to the active arm in the MIRACLE trial, the antiviral activity of lopinavir and ritonavir combination had a EC50 = 8.5 µM, which was similar to that of lopinavir alone with an EC50 = 11.6 µM (p = 0.43), which suggests that lopinavir is the major driver of activity in the combination. The assay data demonstrates that remdesivir (a) and IFNb (e) have superior in vitro antiviral activity compared with the Kaletra combination drug and that ritonavir does not significantly enhance the antiviral activity of lopinavir in vitro.



Clinical

Several detailed reports on clinical experience with lopinavir have been published, though the data are not encouraging. In a study with n=5 patients with COVID-19 in Singapore who received lopinavir/ritonavir, the clinical benefit was not differentiated and disease progressed in n=2. However, a lower dose was used (200/100 mg orally BID) vs. (800mg/200mg QD or BID, per label) of lopinavir/ritonavir. In another study of n=4 patients in Shanghai (n=2 mild disease and n=2 with severe disease), received lopinavir/ritonavir (400/100 mg orally BID for 6-15 days), along with other treatments, including arbidol and traditional Chinese medicine (TCM). N=3 patients improved and n=2 of them had negative viral testing at the end of data collection, while the last patient (with severe COVID-19) showed signs of improvement at the end of data collection.

A recent NEJM published study in 199 patients evaluated lopinavir–ritonavir vs. standard of care. The percentage of patients with detectable RNA over time was similar, no difference was observed in time to clinical improvement (HR of 1.24) and the mortality rate at day 28 was similar between the arms (19.2% in the active arm vs. 25% on standard of care). Study authors concluded that no treatment benefit was observed.

Source: Infectious Disease Alert, Pharmacotherapy Considerations for COVID-19.; Sheahan TP, Nat Commun. 2020 Jan 10;11(1):222.

Kaletra/Aluvia – Ongoing Clinical Trials (Global)

Kaletra (Lopinavir/Ritonavir) is involved in 16 trials globally (includes trials where it is part of control arms), but being evaluated in 8 trials globally. Additional trials in China were attempted but retracted/cancelled, but ClinicalTrials.gov have captured the following:

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04307693	Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	150	Asan Medical Center	South Korea	05/2020
NCT04255017	A Prospective/Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia Deemed of high importance	400	Tongji Hospital	China	06/2020
NCT04261907	Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection	160	First Affiliated Hospital of Zhejiang University / Ascletis Pharmaceuticals	China	05/2020
NCT04252885	The Efficacy of Lopinavir Plus Ritonavir and Arbidol Against Novel Coronavirus Infection	125	Guangzhou 8th People's Hospital	China	05/2020
NCT04315948	Trial of Treatments for COVID-19 in Hospitalized Adults	3200	National Institute for Health and Medical Research (INSERM)	France	03/2023
NCT04276688	Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	70	The University of Hong Kong	Hong Kong	01/2022
NCT04303299	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19 : A Randomized Control Trial	80	Rajavithi Hospital	Thailand	10/2020
NCT02845843	MERS-CoV Infection treated With A Combination of Lopinavir /Ritonavir and Interferon Beta-1b	194	King Abdullah International Medical Research Center	Saudi Arabia	12/2020

Source: Clinicaltrials.gov; ChiCTR

Tamiflu (Oseltamivir) – ROG-SWX

Background and Mechanism

Tamiflu (Oseltamivir) is an influenza neuraminidase inhibitor (NAI).

It is indicated for the treatment of acute, uncomplicated influenza A and B in patients 2 weeks and older who and have been symptomatic for no more than 48 hours. It can also be used as prophylactic management of influenza A and B in patients 1 year and older.

It is manufactured by Genentech/ROG-SWX.

Product Characteristics

- **Oral Capsule**
- **Approved in the US (on the WHO's List of Essential Medicines)**
- **Relatively well tolerated.** Common adverse effects include: Nausea, vomiting, headache and pain. Can be taken without regard to food
- **Available as both capsule formulation and a powder for oral suspension**
- **For adults and those older than 13 years, the recommended dose is 75mg BID for 5 days**
- **Given that the product has approved generics as of 2016, presumably it is cheap and relatively easy to manufacture.**

COVID-19 Status

There are currently no data regarding the use of oseltamivir in nCoV and thus there are only case reports of its use, while ongoing clinical trials will likely share further insights (covered on next slide).

In a single-center case series of 138 hospitalized patients with confirmed NCIP in Wuhan, China, presumed hospital-related transmission of 2019-nCoV was suspected in 41% of patients, 26% of patients received ICU care, and mortality was 4.3%. ~90% of the hospitalized patients (n=124) had received oseltamivir. As of February 3, 47 patients (34.1%) were discharged and 6 died (overall mortality, 4.3%), but the remaining patients are still hospitalized. Among those discharged alive (n = 47), the median hospital stay was 10 days (IQR, 7.0-14.0).

We will watch the results from the 6-Week prospective, open-label, randomized, in multicenter study in Thailand with n=80 stratified by severity and looking at those with mild disease.

Table 4. Complications and Treatments of Patients Infected With 2019-nCoV

	No. (%)			
	Total (N = 138)	ICU (n = 36)	Non-ICU (n = 102)	*P* Value[a]
Complications				
Shock	12 (8.7)	11 (30.6)	1 (1.0)	<.001
Acute cardiac injury	10 (7.2)	8 (22.2)	2 (2.0)	<.001
Arrhythmia	23 (16.7)	16 (44.4)	7 (6.9)	<.001
ARDS	27 (19.6)	22 (61.1)	5 (4.9)	<.001
AKI	5 (3.6)	3 (8.3)	2 (2.0)	.11
Treatment				
Antiviral therapy	124 (89.9)	34 (94.4)	90 (88.2)	.36
Glucocorticoid therapy	62 (44.9)	26 (72.2)	36 (35.3)	<.001
CKRT	2 (1.45)	2 (5.56)	0	>.99
Oxygen inhalation	106 (76.81)	4 (11.11)	102 (100)	<.001
NIV	15 (10.9)	15 (41.7)	0	<.001
IMV	17 (12.32)	17 (47.22)	0	<.001
ECMO	4 (2.9)	4 (11.1)	0	.004

Sources: UpToDate; AdisInsight; Package Insert; Wang D., JAMA. 2020 Feb 7.

Tamiflu – Ongoing Clinical Trials (Global)

Tamiflu (Oseltamivir) is involved in 3 trials globally (includes trials where it is part of control arms), but being evaluated in 2 trials.

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04303299	Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Chloroquine for Treatment of COVID19 : A Randomized Control Trial	80	Rajavithi Hospital	Thailand	10/2020
NCT04255017	A Prospective/Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia	400	Tongji Hospital	China	06/2020

Source: Clinicaltrials.gov; ChiCTR

Ganovo (Danoprevir) – ROG-SWX

Background and Mechanism

Danoprevir is an orally available, second-generation, non-covalent, small-molecule, reversible inhibitor of the hepatitis C virus (HCV) NS3/NS4A protease. It was originated by Array Biopharma (a subsidiary of Pfizer; PFE) and InterMune (a subsidiary of Roche; ROG-SWX) and then later sold to Roche.

The oral formulation is approved and available for HCV infections in China, and clinical development for the same indication is underway in several countries worldwide.

ROG-SWX is also developing a fixed-dose combination (FDC) tablet of ritonavir-boosted danoprevir for the treatment of hepatitis C.

Product Characteristics

Ganovo is the first direct-acting antiviral agent (DAA) developed by a domestic company in China and was approved in June 2018 to treat viral hepatitis C. It was developed by Ascletis and a subsidiary of WuXi AppTec (WuXi STA)

Chinese biotech Ascletis Pharma (HKEX:1672) announced on March 10th progress of the small sample clinical trial of hepatitis C treatment Ganovo (danoprevir) and ritonavir combination therapy on novel coronavirus pneumonia.

Ascletis, the licensee in China, believes that danoprevir in combination with ravidasvir may offer an effective interferon-free regimen for the treatment of HCV. Clinical development for the regimen is underway in Taiwan and in China for COVID-2019 infections.

COVID-19 Status

There is a clinical trial with a small sample size (N=50) assessing an oral Ganovo and ritonavir combination therapy (NCT04291729), led by Dr Hongyi Chen, director of the Ninth Hospital of Nanchang. It obtained approval from the ethics committee of the hospital on February 16, 2020.

One of the treatment groups in this study is the group receiving oral Ganovo and ritonavir combination therapy, in which 10 novel coronavirus pneumonia patients were planned to be enrolled, and 11 patients actually enrolled.

All 11 patients receiving the oral Ganovo and ritonavir combination therapy have been discharged as they are satisfied with the discharge standards under the "Diagnosis and Treatment Program for Novel Coronavirus Infection (Trial Version 6)" issued by the National Health Commission of the People's Republic of China.

Sources: UpToDate; AdisInsight; The Pharma Letter Press Release

Ganovo – Ongoing Clinical Trials (Global)

Ganovo (danoprevir / ASC08 / ITMN-191 / RG7227 / ITMN B) is currently being evaluated in 1 trial in China and in combination with ritonavir and with/without interferon spray inhalation.

The trial is a randomized clinical trial with parallel assignment across the below 5 treatment arms and is assessing rate of composite adverse outcomes over 14 days; that is defined as SPO2 ≤ 93% (without oxygen supplementation), PaO2/FiO2 ≤ 300mmHg OR a respiratory rate ≤ 30 breaths per minute (without supplemental oxygen)

1. Ganovo + ritonavir ± Interferon atomization
2. Long acting interferon (Pegasys)
3. Recombinant cytokine gene-derived protein (Spray inhalation of Novaferon)
4. Lopinavir + ritonavir (Kaletra)
5. Chinese medicines + interferon atomization

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04291729	An Open and Controlled Clinical Trial to Evaluate Ganovo (Danoprevir) Combined With Ritonavir in the Treatment of Novel Coronavirus（2019-nCoV) Infection	50	The Ninth Hospital of Nanchang / Ascletis Pharmaceuticals Co., Ltd.	China	03/2020

Source: Clinicaltrials.gov; ChiCTR

Xofluza (Baloxavir Marboxil) – ROG-SWX

Background and Mechanism

Xofluza (Baloxavir Marboxil) is a polymerase acidic (PA) cap-dependent endonuclease inhibitor.

It was recently approved in 2018 as a selective inhibitor of influenza cap-dependent endonuclease, an essential enzyme for viral replication (Hayden et al., 2018). Although baloxavir was found to have potent activity against a variety of influenza viruses, variants of influenza with amino acid substitutions at position 38 of the polymerase acidic protein (PA/I38X) produced up to 60-fold higher EC50s to baloxavir in vitro; the incidence of this treatment-emergent PA/I38X substituted variant in adults is 2.2% to 11% (Xofluza, 2018), while a pediatric-focused study showed a relatively higher frequency at 23.4% (Takashita et al., 2018).

It is manufactured by Genentech/ROG-SWX.

Product Characteristics

- **Oral Tablet**
- **Approved in the US for the treatment of acute uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours and are otherwise healthy or at a high risk of developing influenza-related complications.**
- **Relatively well tolerated.** Common adverse effects include: diarrhea (3%), bronchitis (3%), nausea (2%), sinusitis (2%) and headache (1%). Can be taken without regard to food.
- **For patients who weigh <80kg, the recommended dose is two 20 mg tablets taken within 48 hours of symptom onset. If over 80kg, take two 40mg tablets together.**

COVID-19 Status

Currently, there is no data publicly available in regards to Xofluza's efficacy for COVID-19; however, it is being trialed in China along with favipiravir, which we cover later.

Cipla has a partnership with the Council of Scientific & Industrial Research-Indian Institute of Chemical Technology to scale up the stockpile of antiviral compounds such as favipiravir, remdesivir and baloxavir.

_____

Trials conducted for influenza include the CAPSTONE studies. CAPSTONE-1 was a phase 3 trial in otherwise healthy patients (≥12 years old) with uncomplicated influenza that demonstrated baloxavir significantly reduced viral titers and time to alleviation of symptoms (TTAS) when compared to placebo. The clinical benefit of baloxavir was observed regardless of the PA/I38X variants status (Hayden et al., 2018), and there was no clear association between emergence of PA/I38X variants and exacerbation of clinical outcomes.

CAPSTONE-2 was a phase 3 trial in high-risk patients with uncomplicated influenza which demonstrated that baloxavir was well-tolerated and associated with faster recovery and reduced risk of complications in high-risk influenza patients when compared to placebo. Baloxavir was superior to oseltamivir in shortening the duration of viral shedding of influenza A and B virus and in resolving influenza B-associated illness (Ison et al., 2018). PA/I38X variants were found in 5.2% (15/290) of patients enrolled in this study, but emergence of PA/I38X did not result in longer time to improvement of influenza symptoms (Portsmouth, 2019).

Sources: UpToDate; AdisInsight; Package Insert; Beigel et al, Antiviral Research Volume 167, July 2019, Pages 45-67.

Xofluza – Ongoing Clinical Trials (Global)

Xofluza (baloxavir marboxil) is currently being evaluated in China; there are two randomized clinical trials with parallel assignment across 3 treatment arms (2 active and 1 control) assessing both baloxavir marboxil and favipiravir, with one trial evaluating both in combination with the backbone of "current antiviral treatment" while the other compares the treatments with lopinavir/ritonavir.

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
ChiCTR2000029544	A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy	30	The First Hospital Affiliated to Zhejiang University's Medical School	China	5/31/2020
ChiCTR2000029548	Randomized, open-label, controlled trial for evaluating of the efficacy and safety of Baloxavir Marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients	30	The First Affiliated Hospital, Zhejiang University School of Medicine	China	6/03/2020

Source: Clinicaltrials.gov; ChiCTR

ASC09 – ASCLF

Background and Mechanism

Ascletis Pharma (ASCLF), a company in Hong Kong, said it received approval for clinical trials of its ASC09 fixed-dose combination with Ritonavir (ASC09F) to treat coronavirus pneumonia. Upon our review, there are currently two clinical trials ongoing in China; they are expected to have primary completion dates in May 2020 and thus we would expect results on its efficacy and safety then.

ASC09 is being evaluated in 2 trials in China. There was an additional trial (ChiCTR2000029759), but it was retracted due to a "lack of patient[s]".

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04261907 ChiCTR2000029603	Evaluating and Comparing the Safety and Efficiency of ASC09/Ritonavir and Lopinavir/Ritonavir for Novel Coronavirus Infection	160	First Affiliated Hospital of Zhejiang University / Ascletis Pharmaceuticals	China	05/2020
NCT04261270	A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC09F and Ritonavir for 2019-nCoV Pneumonia	60	Tongji Hospital	China	05/2020

Sources: UpToDate; AdisInsight

DAA discovery program – ENTA

Background / Status

Enanta Pharma (ENTA) announced on March 13th, 2020 that it has initiated a two-pronged approach to its COVID-19-related efforts:

1. There is a drug discovery program that is leveraging its experience with direct-acting antiviral drug mechanisms and candidates along with its overall virology know-how.
2. Secondly, the company is also screening compounds from its antiviral compound library for potential activity against COVID-19.

ENTA has experience with developing antiviral drugs from its collaboration with ABBV on Glecaprevir, a protease inhibitor that ENTA discovered. It is currently marketed by ABBV as Mavyret for the treatment of chronic HCV infection.

The company additionally has worked on the discovery of another direct-acting antiviral compound, pibrentasvir, which is part of the fixed-dose combination drug Mavyret with Glecaprevir.

Source: Company reports, Guggenheim Securities

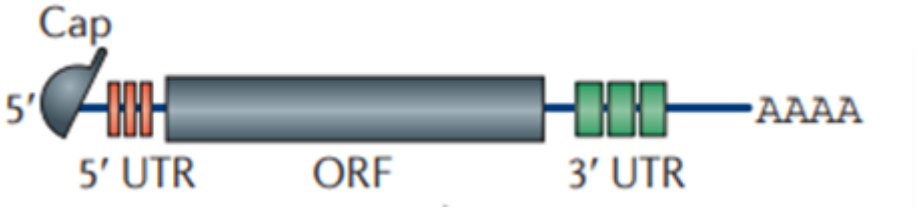
Vaccines for the treatment of COVID-19

1. mRNA vaccines
2. Other vaccine approaches

mRNA vaccine Overview

Recall the central dogma of biology: hard coded genetic information (DNA) is transcribed into transportable, temporary cassettes, known as messenger RNA (mRNA), and each mRNA cassette contains the “recipe” for synthesis of a particular protein (or small number of proteins). mRNA-based vaccine approaches mimic the immune response induced by its mRNA encoded proteins. They also utilize the body’s own biology to “self-manufacture” the vaccine, thus share the same pharmacology to endogenous mRNA. Instead of having to manufacture large amounts of protein in a factory to provide a dose to each patient, mRNA given to a subject is used as a template for the body to essentially self-vaccinate.

Messenger RNA (mRNA)



mRNA coded proteins are degraded by various pathways into either amino acids or antigenic peptide epitopes that can induce a virus-specific T cell response. The degraded antigenic peptide epitopes are loaded onto major histocompatibility complex (MHC) molecules that are expressed on the surface of healthy cells to mark what cells are “self” vs. foreign. These MHCs express protein-derived epitopes on the cell surface to generate an immune response.

What are the benefits of a mRNA-based vaccine?

- There are currently no approved mRNA-based therapies for any use (vaccines or otherwise). However, animal models are encouraging, showing immunization after 1-2 doses, and there are multiple mRNA-based vaccines in development.
- Recall that the proteins are degraded into **antigenic peptide epitopes** that can induce a virus-specific T cell response. Three approaches currently in the clinic: 1) mRNA encoding combinations of viral proteins; 2) two component vaccines containing mRNA adjuvant and mRNA encoding antigen, and; 3) self-amplifying mRNA with sequences of positive-stranded RNA viruses.
- mRNA vaccines can be made at a faster timescale compared to conventional vaccine production (weeks instead of months) as mRNA can be produced using a using a cell-free system without cellular or animal components involved. However, because mRNA-based medicines are new (without an approved or commercialized product), manufacturing capabilities may vary depending on the manufacturer.

Source: Türeci et al. 2014. mRNA-based therapeutics--developing a new class of drugs, Company reports, Guggenheim Securities, LLC Research

mRNA-1273 – MRNA

Background and Mechanism

mRNA-172 is an mRNA-based vaccine in development. Its MRNA candidate encodes for a full-length, prefusion stabilized form of the Spike (S) protein and is encapsulated by lipid nanoparticles.

Moderna's mRNA vaccine platform includes 9 prophylactic vaccines in development. Its vaccine candidates has demonstrated positive Phase 1 readouts in 6 prophylactic vaccines – H10N8, H7N9, RSV, chikungunya virus, hMPV/PIV3 and CMV. Its latest stage vaccine program is its CMV program in Phase 2 studies.

MRNA/NIH have previously collaborated on a vaccine for MERS, which remained in the research stage.

Product Characteristics

- **I.M. injection.** The Phase 1 study is evaluating 3 dose cohorts: 25 microgram, 100 mcg, or 250 mcg. Patients will receive two doses in the deltoid ~28 days apart

MRNA has stated that it can produce >10+ million doses per year. MRNA built and operationalized its internal fully integrated 200k sq ft Norwood, MA facility in 22 months. MRNA is scaling production to manufacture millions of doses per month, in the potential form of individual or multi-dose vials.

Current Status / Commentary

mRNA-1273 is currently being evaluated in a Phase 1 study (NCT04283461) in healthy adults.

This mRNA vaccine was designed and manufactured in 25 days: the NIH finalized the sequence on Jan 13th, 2 days after the Chinese government release the sequence, following which MRNA began manufacturing. The first clinical batch was completed Feb 7th and the shipped to the NIH on Feb 24th. The FDA completed its IND review on March 4th, and the first patient was dosed in the Phase 1 trial on March 16th. The full development timeline is available on MRNA's website.

While the NIH has conducted preclinical testing in mice (not yet published) showing a "potent antibody response", they emphasized that Phase 1 testing was based on a safety assessment based on prior human studies of other mRNA-based vaccines. Additional animal studies (mice and NHP), in addition to data from the Phase 1, are underway and will establish the rationale for testing the vaccine in larger trials if warranted. – NIAID statement, 18th March 2020.

The Phase 1 study is expected to enroll ~45 healthy adults over 6 weeks. The study is enrolling patients at the Kaiser Permanente Washington Health Research Institute in Seattle, with Jennifer Halle as the first patient injected (see the Time interview here). As of March 19th, Kaiser Permanente noted that study recruitment was closed.

MRNA is preparing for a potential Phase 2 study under its own IND, which "could begin in a few months", and manufacturing is already underway.

At a competitor conference on March 20th, CEO Bancel described a ~12-18 month timeline for a commercially-available vaccine, with the potentially for an earlier, emergency vaccine available to some people such as healthcare professionals in the fall of 2020.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

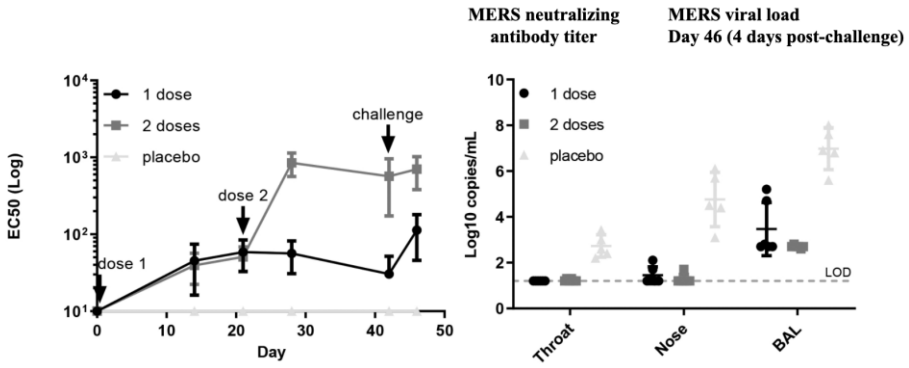
mRNA-1273 – MRNA's infectious disease program readthrough

Moderna currently has 9 development candidates in its prophylactic vaccines modality. This includes respiratory viruses, including two pandemic influenza strains, RSV, hMPV, and PIV3, infections that transmit from mother-to-baby, including CMV and Zika, and highly prevalent viral infections, such as EBV. The company has dosed >1,000 healthy volunteers from 9 Phase 1 vaccine trials at dose levels up to 400µg, and the safety and tolerability profile has appeared consistent with marketed adjuvanted vaccines.

MRNA has demonstrated positive Phase 1 data readouts as measured by neutralizing antibodies to the viral antigen from 6 prophylactic vaccines (H10N8, H7N9, RSV, chikungunya virus, hMPV/PIV3 and CMV), while mRNA-1325, its initial Zika vaccine, did not (instead the company is advancing mRNA-1893, its next-gen Zika vaccine).

Modality	ID #	Program *Indication*	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Core modalities							
Prophylactic vaccines	**mRNA-1647**	Cytomegalovirus (CMV) vaccine					Worldwide
	mRNA-1893	Zika vaccine					Worldwide *BARDA funded*
	mRNA-1172	Respiratory syncytial virus (RSV) vaccine					**Merck** to pay milestones and royalties
	mRNA-1777	Respiratory syncytial virus (RSV) vaccine					
	mRNA-1653	Human metapneumovirus and parainfluenza virus 3 (hMPV/PIV3) vaccine	Phase 1 (healthy volunteers)	Phase 1b (seropositives)			Worldwide
	mRNA-1345	Pediatric respiratory syncytial virus (RSV) vaccine *Future respiratory combo*					Worldwide
	mRNA-1851	Influenza H7N9 vaccine					Worldwide *Advancing subject to outside funding*
	mRNA-1189	Epstein-Barr virus (EBV) vaccine					Worldwide
	mRNA-1273	Novel coronavirus (SARS-CoV-2) vaccine					Worldwide *CEPI funded*

The MRNA/NIH have previously collaborated on a vaccine for MERS, another species of coronavirus. Similar to COVID-19, MERS also contains a Spike protein complex that is necessary for membrane fusion and host cell infection. In its collaboration with the NIH, MRNA designed an mRNA-based vaccine targeting the prefusion-stabilized Spike protein for MERS. In a rabbit model, the vaccine led to the induction of nAbs that resulted in a ~3-log reduction in viral titers in the nose, and ~4-log reduction in viral titers detected from bronchoalveolar lavage. Viral titers in the throat were reduced to the lower limit of detection.



Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

mRNA vaccine (CV7202) – CureVac

Background and Mechanism

CureVac is developing an mRNA-based vaccine in collaboration with Duke-NUS to develop a Coronavirus (COVID-19) vaccine. CureVac's mRNA-based vaccines focus on optimizing the UTR and ORF chemistry while maintaining unmodified nucleosides. Its vaccines are encapsulated by lipid nanoparticles.

While details on its COVID-19 vaccine are light, the company does have other vaccine programs ongoing including its clinical-stage Rabies program and preclinical stage influenza program. Results from its Phase 1 study evaluating CV7202, its 2nd-gen rabies vaccine in healthy volunteers showed an immune response at its lowest 1 µg dose cohort.

Current Status / Commentary

CureVac's mRNA vaccine is currently in preclinical stages of development.

Product Characteristics

- **I.M. delivery**

CureVac has a production suite in Tübingen, Germany, which includes GMP qualifications for 3 suites while a 4th suite in under construction. The company notes it is building out capacity to "produce up to 30 million doses of RNA-based therapeutics per year." CureVac has stated that it can produce "up to ten million vaccine doses in one production run", and noted that it is working "on expanding its manufacturing capacities to be able to provide up to billions of doses for outbreak situations like Covid-19".

In addition, the company's RNA Printer "is capable of producing several grams of LNP-formulated mRNA (enough to produce more than a hundred thousand doses), within just a few weeks".

COVID-19 Status

CureVac is currently selecting candidates from several constructs. It has noted that it is working to accelerate development with the German Paul Ehrlich Institute and other European health authorities, and the company expects to start clinical trials in early summer 2020.

The company noted during its March 17th 2020 conference call (replay here) that it has two vaccine candidates and that it is awaiting animal data.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

CV7202 – Relevant Data Summary

CV7202 Rabies Vaccines Readthroughs

CureVac's lead vaccine program is its CV7202 vaccine for rabies. Its legacy CV7201 reported results in 2017. Its 2nd gen CV7202 program utilizes optimized mRNA technology (optimized UTR and ORF) formulated with lipid nanoparticles.

Results from the 1st gen program CV7201.

CureVac conducted Phase 1 study (NCT02241135) in healthy volunteers for its Rabies vaccine CV7201 in which 101 healthy volunteers received a 80–640 µg dose three times by either needle-syringe or needle-free devices, either intradermally or intra-muscularly. Results published in Lancet in 2017 showed that patients dosed with needle-free devices demonstrated neutralizing antibody titers of 0·5 IU/mL or more in 32 (71%) of 45 participants given 80 µg or 160 µg CV7201 doses intradermally and six (46%) of 13 participants given 200 µg or 400 µg CV7201 doses intramuscularly. Needle-syringe injection did not show the same effect, with only 1 participant (320 µg intradermally) showing a detectable immune response.

Results from the 2nd gen CV7202 program.

CV7202 is being evaluated in a Phase 1 study (NCT03713086) in 53 healthy volunteers. The open-label, dose-escalation study was originally designed to evaluate 1 or 2 intramuscular doses of the vaccine at days 1 and 29 at 6 dose levels – in January 2020 CureVac reported interim results in which the lowest dose cohort (two doses of 1 µg mRNA vaccine) induced an adaptive immune response with virus-neutralizing antibody titers above the WHO's recommended threshold. Further results are expected at a scientific conference.

Other infectious disease programs

CV7301 Influenza Vaccines Readthrough

CureVac is developing CV7301, a 2nd gen LNP influenza vaccine. The company has completed NHP studies that the company notes "has demonstrated strong and durable immunogenicity in non-human primates." Additional information is not available.

CEPI partnership

CureVac and the Coalition for Epidemic Preparedness Innovations (CEPI) entered into a partnership in February 2019 for the development of LNP, mRNA-based vaccines for known pathogens and new and previously unknown pathogens. The agreement initially included preclinical development of vaccines for Lassa Fever, Rabies, and Yellow fever. This partnership was expanded in January 2020 to develop a vaccine for COVID-19.

Bill and Melinda Gates Foundation

The Bill and Melinda Gates Foundation made an initial $52 million equity investment in March 2015 to development mRNA-based vaccines. The Foundation then awarded additional grants in February 2018 for the development of prophylactic vaccines for influenza and malaria infection.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

BNT162 – BNTX, Fosun Pharma (China), PFE (ex-China)

Background and Mechanism

BioNTech is developing BNT162, an mRNA-based vaccine in development to induce immunity and prevent Coronavirus (COVID-19) infection. The company has partnered with Fosun Pharma to develop BNT162 in China and with PFE to co-develop in ex-China regions.

BNTX's mRNA vaccine platform include uridine-containing mRNA (uRNA), nucleoside modified mRNA (modRNA), self-amplifying mRNA (saRNA), and trans-amplifying mRNA (taRNA) – we've discussed these in more details in our PubMed PreGame series here. The company uses modified mRNA in its mRNA approaches. The company has not specified details around its program,

BNTX's vaccine portfolio also includes its influenza partnership with PFE, partnership with Penn's Drew Weissman, and R&D agreement with the Bill and Melinda Gates Foundation to develop vaccines for HIV and tuberculosis.

Product Characteristics

- **LNP encapsulation**
- **While BNTX has not disclosed the mRNA format of BNT162, we note BNT161 utilizes its saRNA platform, which potentially allows a higher response at a lower dose.**

BTNX is responsible for manufacturing BNT162. The company has 4 facilities to support discovery, formulations, and GMP manufacturing.

Current Status / Commentary

BNT162 is currently in preclinical stages of development.

COVID-19 Status

BNT162 is currently in preclinical stages of development. The company expects to begin clinical testing in late April.

The company noted it has been in contact with global regulatory agencies and is planning a global clinical development program in Europe (commencing in Germany), the United States and China.

BNTX/PFE noted that they plan to "utilize multiple research and development sites from both companies, including in the United States and Germany, to house the activities identified by the collaboration agreement."

BNTX and Fosun Pharma will jointly conduct clinical trials in China. Upon regulatory approval, Fosun Pharma will commercialize the vaccine in China.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

BNT162 – Relevant Data Summary

mRNA platform

BioNTech highlights several mRNA formats it could utilize for BNT162:

- **Optimized Uridine mRNA (uRNA).** uRNA is optimized for immunogenicity by optimizing uridine for activation of immune sensors, improving MHC presentation.
- **Nucleoside-modified mRNA (modRNA).** modRNA incorporates modified nucleosides to reduce immunogenic reactions.
- **Self-amplifying mRNA (saRNA).** saRNA encode the protein of interest like conventional mRNA, as well as a replicase polymerase that multiplies the mRNA within the target cell. This allows for higher levels of sustained antigen production at lower doses.
- **Trans-amplifying mRNA (taRNA).** taRNA divides the job of saRNA into two pieces: vaccine antigen and replicase components.

Infectious disease programs

BNT161 influenza vaccines

BioNTech and PFE are co-developing BNT161, an mRNA-based vaccine for influenza. BNTX and PFE entered into a collaboration agreement in August 2018. BNT161 will encode influenza virus antigens selected by the WHO in advance of the flu season and will utilize BNTX's self-amplifying mRNA platform encapsulated by LNPs. The program is currently in preclinical development, and the company expects to begin clinical development in 2H20.

Penn partnership

BioNTech and the University of Pennsylvania (Drew Weissman's lab) entered into a partnership in November 2018 for the development of nucleoside-modified mRNA-based vaccines for up to 10 disease candidates. Penn will be responsible from discovery through to the completion of IND-enabling studies, after which BNTX will have an option to license the candidates. The company expects to begin its first Phase 1 study in 2021.

Bill and Melinda Gates Foundation

BNTX and the Bill and Melinda Gates Foundation entered into an agreement to develop mRNA-based vaccines for HIV and tuberculosis in September 2019, which includes an initial equity investment of $55M.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

mRNA vaccine – ARCT

Background and Mechanism

ARCT is developing an mRNA-based vaccine in collaboration with Duke-NUS to develop a Coronavirus (COVID-19) vaccine. Its vaccine utilizes STARR (Self-Transcribing And Replicating RNA) that encodes not only the antigen but also the viral replication machinery (replicase polymerase), allowing for high antigen production at low doses of vaccine.

ARCT management indicated that based on pre-clinical work its STARR technology can be dosed at a multiple fold lower dose than other mRNA-based vaccines, and given the sustained expression seen in mice, there is potential that a booster dose would not be needed.

ARCT has experience developing vaccines through its partnerships, including an undisclosed partnership with a vaccine company, relations with animal health companies, and its personalized cancer vaccine partnership.

Product Characteristics

- **I.M. delivery**
- **STARR platform.** ARCT"s self-replicating mRNA encodes the protein of interest like conventional mRNA, but also encodes a replicase polymerase that multiplies the mRNA within the target cell. This produces a double-stranded RNA intermediate that can trigger an immune response from a small level of initial mRNA.
- **Microgram doses.** ARCT noted that it expects doses in the single microgram dose range, with the potential that a booster would not be needed.

ARCT has stated that it can produce a double digit gram drug substance in less than a week. Given the single microgram dose, it believes a single batch (pending dosing/trials) could potentially vaccinate the whole Singapore population.

Current Status / Commentary

ARCT's mRNA vaccine is currently in preclinical development.

COVID-19 Status

ARCT's mRNA vaccine is currently in preclinical development. During its 4Q19 call, ARCT noted that the company has already chosen the target for its COVID-19 vaccine program and is in the process of development/scale up to provide material to the Singaporean government for initial testing.

Dr. Ooi Eng Eong, deputy director of the Duke-NUS's emerging infectious diseases program, commented to Reuters in an article published March 24th, 2020 that mice studies would start in ~1 week and human clinical trials are expected in 2H20.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

mRNA vaccine – Fudan University, Shanghai JiaoTong University, RNACure Biopharma

Background and Mechanism

Fudan University, Shanghai JiaoTang University, and RNACure are collaborating to develop a COVID-19 mRNA-based vaccine. The groups announced its joint research collaboration on March 7th, 2020 and plan to use two methods: 1) to use mRNA to express the receptor-binding spike protein of COVID-19 to induce nAbs; and 2) to use mRNAs to produce virus-like particles (VLPs) with features (morphological and structural) similar to COVID-19 viruses to activate immune responses. The group noted that they are more focused on option 2 given the similar efficacy between VLPs and live attenuated viruses but more optimal safety profile. The group has formulated an mRNA cocktail containing three genes of COVID-19 to produce VLPs.

Current Status / Commentary

Fudan University, Shanghai JiaoTang University, and RNACure's mRNA-based vaccine is in preclinical development.

Product Characteristics

- **mRNA cocktail containing 3 genes of COVID-19 to produce VLPs.**
- **Additional details around the program have not been disclosed, to our knowledge.**

COVID-19 Status

Fudan University, Shanghai JiaoTang University, and RNACure's mRNA-based vaccine is in preclinical development.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

mRNA vaccine – Chinese Centre for Disease Control and Prevention, Tongji University School of Medicine, Stermirna Therapeutics

Background and Mechanism

The Chinese Centre for Disease Control and Prevention, Tongji University School of Medicine, and Stermirna Therapeutics are developing an mRNA-based vaccine. The program was announced on January 28, 2020 and is currently in preclinical development. Stermirna CEO Li Hangwen stated that "no more than 40 days will be needed to manufacture the vaccine samples based on the new generation of mRNA technology and some preliminary procedure."

Current Status / Commentary

The mRNA vaccine is currently in preclinical development.

Product Characteristics

- **Details around the program have not been disclosed, to our knowledge.**

COVID-19 Status

The mRNA vaccine is currently in preclinical development. Initial mice testing began on February 9th, per Xinhua, and the group plan to conduct studies in larger animal models prior to clinical testing. Clinical testing is expected begin mid-April, per yicai.com

In an interview by thepaper.cn, Stermirna's chief executive Li Hangwen noted that the vaccine could arrive on the market in 2020 if its first-phase clinical trials went smoothly.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

saRNA Vaccine – Shattock Lab (Imperial College London)

Background and Mechanism

Self-amplifying RNA (sa-RNA) vaccines are derived from alphaviruses, which are positive-strand, non-segmented RNA viruses. RNA vaccines have demonstrated versatility in many animal models of infectious and non-infectious diseases. Self-amplifying RNA replicons encode genes drive their amplification within the cytoplasm of host cells. As such, sa-RNA vaccines have the potential to be more effective than corresponding mRNA vaccines.

Compared with the rapid expression of conventional mRNAs, published results have shown that vaccination with self-amplifying mRNA vaccines results in higher antigen expression levels, although delayed in time, which persist for several days *in vivo*.

Product Characteristics

Self-amplifying RNA vaccines

Administered as naked RNA packaged in viral particles, or delivered by electroporation in situ

- **Advantages** include:
  - Safety - less risk of integration into genome of immunized host than DNA vaccines
  - Directly translated in cytoplasm; no need for nuclear delivery and subsequent transcription
- **Limitations** include:
  - Challenges in delivery of RNA vaccines, particularly as a potentially widely used prophylactic against coronavirus infection

Current Status

The Shattock Lab's COVID-19 self-amplifying RNA vaccine is not approved anywhere for use.

Clinical trials of mRNA vaccines for infectious diseases are in their early stages, with trials conducted with mRNA encoding HIV-1 antigens and human cytomegalovirus having shown safety and antigen-specific immune responses.

Self-amplifying RNA vaccines have not been evaluated for any coronaviruses in preclinical or clinical studies.

COVID-19 Status

Professor Robin Shattock and his team in Imperial College London's Department of Infectious Disease developed a candidate vaccine within 14 days of getting the sequence from China.

The lab began testing the vaccine on animals on February 10 and plans to move to clinical trials in the summer.

The Shattock Lab COVID-19 vaccine is not currently being evaluated in any clinical trials.

Source: Guggenheim Securities LLC Research

MVA-encoded VLP Vaccine – GOVX/ BravoVax

Background and Mechanism

Modified Vaccinia Ankara (MVA) vaccines are considered to be safe vaccine platforms with the advantage of being a live replication-competent vector in avian cells for manufacturing, but replication-deficient in mammalian cells for vaccination. Importantly, MVA vaccines elicit protective T cell as well as antibody responses in animals and humans.

Virus Like Particles (VLPs) can be used to express proteins in their native conformations, enabling construction of immunogenic vaccine candidates that induce full protection after a single dose. Because no live virus is involved in the manufacturing process, VLPs can be easily generated in a low-containment manufacturing environment.

Product Characteristics

MVA vaccines

Jynneos MVA vaccine is administered through subcutaneous injection

- **Advantages** include safety and proven clinical efficacy as a vaccine platform for MERS-CoV
- **Disadvantages** include that MVA vaccines have yet to be approved for prevention of coronaviral infections.

VLPs

- **Advantages** include safety due to the inability to replicate, as well as the proven ability to elicit strong T cell and B cell immune responses. VLP technology has been applied in several approved vaccines, including the blockbuster Gardasil &Gardasil 9 HBV vaccines
- **Disadvantages** are that the expression system may limit effectiveness of VLPs, and VLPs have yet to be approved for prevention of coronaviral infections.

Current Status

The MVA vaccine platform is used in the commercially available Jynneos smallpox vaccine, has been used in numerous preclinical and clinical trials as a vaccine vector against several infectious diseases, including MERS-CoV and Zika.

Several VLP-based vaccines are commercially available including vaccines against Human Papilloma Virus (HPV) such as Cervarix, Gardasil & Gardasil9 and Hepatitis B Virus (HBV) including the 3rd generation Sci-B-Vac. In addition, the first licensed malaria-VLP-based vaccine Mosquirix has been approved by the European regulators.

COVID-19 Status

On January 17 2020 GeoVax and BravoVax signed a Letter of Intent to jointly develop a vaccine against COVID-19.

GeoVax will use its MVA-VLP vaccine platform to design and construct the vaccine candidate using genetic sequences from the ongoing coronavirus outbreak originating in Wuhan, China. BravoVax will provide further development, including testing and manufacturing support, as well as direct interactions with Chinese public health and regulatory authorities.

MVA-VLP is not currently being evaluated in any clinical trials.

Source: Guggenheim Securities LLC Research

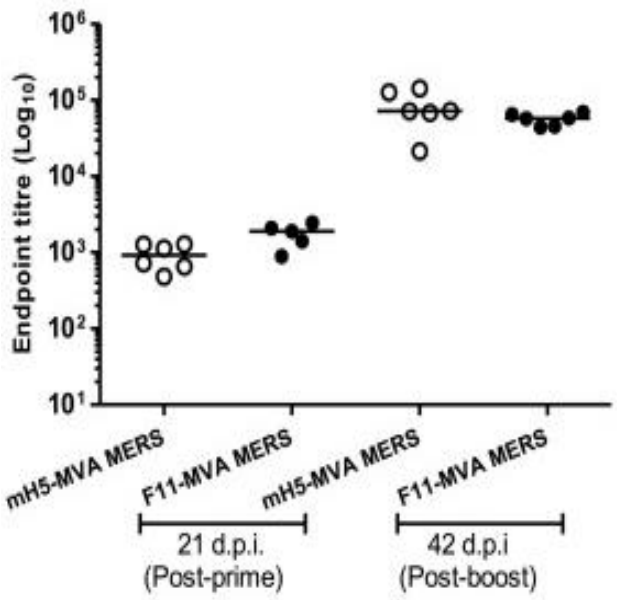
MVA Vaccines Relevant Preclinical Data

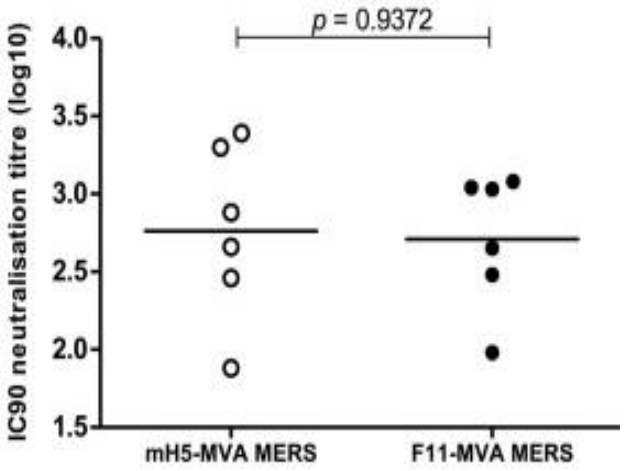
MVA-VLP COVID-19 vaccine does not yet have any published preclinical or clinical data. MVA based vaccine candidates against MERS-CoV have been tested in preclinical animal studies, showing the ability to elicit neutralizing antibodies and cellular immune response.

Four vaccine candidates against MERS-CoV based on ChAdOx1 and MVA viral vectors were developed containing the full-length spike gene of MERS-CoV and evaluated in a mouse model in prime only or prime-boost regimens. A single dose of ChAdOx1 MERS with tPA elicited cellular immune responses as well as neutralizing antibodies that were boosted to a significantly higher level by MVA MERS.

Humoral and cellular immunogenicity of homologous MVA MERS vaccination in BALB/c mice

- BALB/c mice (n = 6) were immunized intramuscularly with 1 × 10^6 pfu MVA MERS, in a homologous prime-boost vaccination with three-weeks interval between vaccination.
- At 21 d.p.i. F11-MVA MERS and mH5-MVA induced similar levels of S1-specific antibodies (mean endpoint titer (Log10) = 3.2 and 2.8 respectively
- The protective level of either antibodies or cellular immunity required to counter MERS-CoV infection in humans or in animal models is not yet defined





Source: Alharbi et al Vaccine 2017, Guggenheim Securities LLC Research

Medicago's Plant-based VLP Vaccine

Background and Mechanism

Virus-like particles (VLPs) are nanoscale particles that mimic the native structure of viruses, allowing them to be recognized by the immune system, but lack core genetic material which makes them non-infectious and unable to replicate. Because no live virus is involved in the manufacturing process, VLPs can be easily generated in a low-containment manufacturing environment.

Medicago's plant-based VLP production platform may allow scalable shortening of production timeline over traditional egg-based production systems to produce clinical-grade prophylactics.

Current Status

Medicago's COVID-19 VLP vaccine is not approved anywhere for use.

Medicago has proven ability to advance a VLP vaccine candidate through clinical trials for influenza. The company's plant-derived quadrivalent VLP influenza vaccine has demonstrated safety and immunogenicity profile in adults, including those over the age of 65 years.

Through work of other research groups and companies, several VLP vaccines and chimeric VLPs against MERS-CoV and SARS-CoV have been developed and assessed in preclinical studies.

Product Characteristics

Plant-based production platform

- Rapid (6-8 week production timelines) and scalable with capacity adjustable to market needs with versatile applications
- However, the platform is relatively unproven and has yet to produce a licensed vaccine

VLPs

- **Advantages** include safety due to the inability to replicate, as well as the proven ability to elicit strong T cell and B cell immune responses. VLP technology has been applied in several approved vaccines, including the blockbuster Gardasil &Gardasil 9 HBV vaccines
- **Disadvantages** are that the expression system may limit effectiveness of VLPs, and VLPs have yet to be approved for prevention of coronaviral infections.

COVID-19 Status

On March 12 Medicago announced production of its COVID-19 VLP vaccine candidate 20 days after receiving the SARS-CoV-2 gene. The vaccine is now in production in preparation for preclinical safety and efficacy testing.

On March 21 Medicago announced at $7M contribution from the Government of Quebec towards the company's COVID-19 vaccine development. The company anticipates the beginning of human trials by July or August 2020.

Medicago's COVID-19 VLP is not currently being evaluated in any clinical trials.

Source: Guggenheim Securities LLC Research

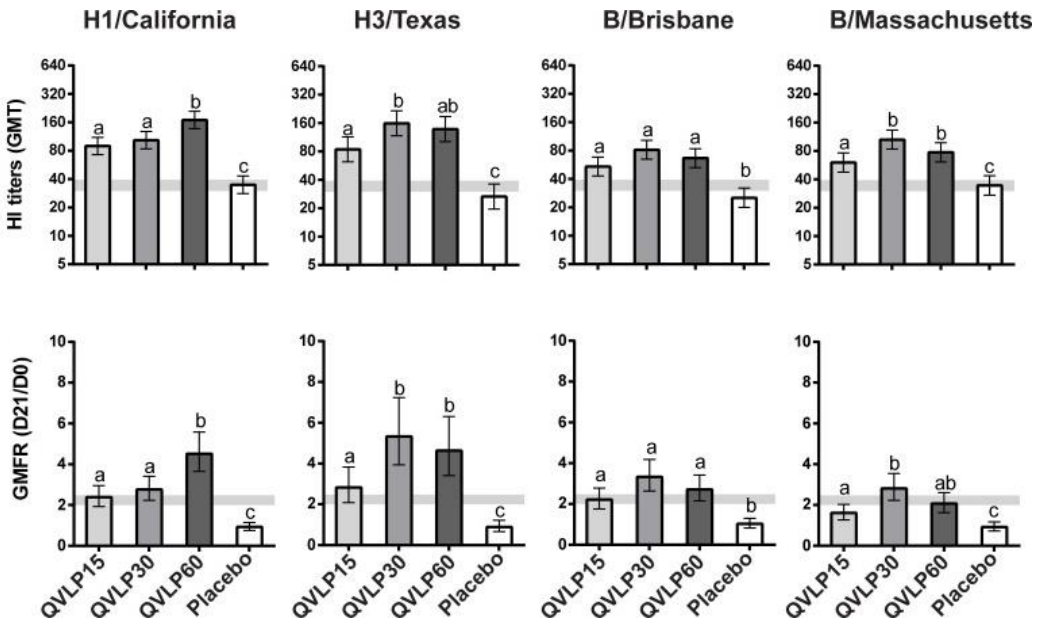
Medicago's VLP Vaccine Relevant Preclinical Data

Medicago's COVID-19 VLP vaccine does not yet have any published preclinical or clinical data. However, Medicago's leading product, a seasonal recombinant quadrivalent VLP vaccine for active immunization against influenza, is currently under review by Health Canada following the completion of its clinical program.

Immunogenicity and safety of Medicago's quadrivalent VLP vaccine for influenza were assessed in two Phase II trials. In the first Phase II trial (NCT02233816), 18–49 year old subjects received 15, 30 or 60 µg/strain of a hemagglutinin-bearing quadrivalent virus-like particle (QVLP) vaccine or placebo. In the second trial (NCT02236052), ≥50 years old subjects received QVLP as above or placebo with additional groups receiving 7.5 or 15 µg/strain with alum.

In older adults ≥50 years, Medicago's QVLP vaccine produced significantly higher serum antibody response (HI titers) and geometric mean fold rise (GMFR) than placebo in four influenza strains.

- QVLP vaccine was produced in *N. benthamiana* using the Agrobacterium infiltration-based transient expression platform and injected at 15, 30 or 60 µg HA equivalent per strain
- HA proteins in the VLP were based on human sequences of A/California/07/2009 H1N1 (H1/Cal), A/Victoria/361/11 H3N2 (H3/Vic), B/Brisbane/60/08 (B/Bris, Victoria lineage) and B/Massachusetts/02/2012 (B/Mass, Yamagata lineage) influenza strains
- The addition of alum adjuvant did not significantly improve the Ab response



Source: Pillet et al PLoS One 2019, Guggenheim Securities LLC Research

VLP Vaccines Relevant Preclinical Data Summary

Several promising subunit vaccines against MERS-CoV have been developed and assessed in preclinical studies.

Early MERS-CoV VLPs produced in a baculoviral expression system have generated neutralizing antibodies and produced protective efficacy in viral challenge animal studies. Chimeric VLPs for MERS-CoV have also been generated displaying the S protein of MERS-CoV and matrix 1 protein of influenza A virus which have shown to be immunogenic in mouse models. However, the actual protective efficacy of these cVLPs against MERS-CoV has yet to be investigated in vivo.

MERS antigen	ROA	Results	Reference
MERS-CoV VLPs	IM	Co-administration of the VLPs-based vaccine and alum activated RBD specific humoral and cellular immune responses in rhesus macaques.	Wang et al., 2017b
S protein nanoparticles	IM	S protein produced in the baculovirus insect cells expression system assembled into nanoparticles of approximately 25 nm. Mice immunized with these nanoparticles in the presence of alum produced high titer of neutralizing antibody.	Coleman et al., 2014
S protein nanoparticles	IM	The vaccine together with Matrix M1 adjuvant activated S protein specific humoral immune responses, and protected hDPP4 transduced mice against viral challenge.	Coleman et al., 2017
CPV VLP displaying RBD	IM	Immunization of the mice with the chimeric VLPs displaying RBD in the presence of adjuvants [alum or Poly(I:C)] elicited neutralizing antibody responses as well as cellular immune responses.	Wang et al., 2017a
Influenza A VLP displaying S protein	IM	Immunization of the mice with the chimeric VLPs displaying RBD in the presence of a combination of adjuvants (alum and CpG ODN) elicited neutralizing antibody responses.	Lan et al., 2018

Source: Yong et al Front Microbiol 2019, Guggenheim Securities LLC Research

University of Queensland Subunit Vaccine

Background and Mechanism

University of Queensland's (UQ) molecular clamp technology (MCT) is a platform technology that facilitates expression of recombinant viral glycoproteins in their native pre-fusion subunit form without loss of native antigenicity.

The molecular clamp allows for stabilization of the protein form expressed on the virion surface as the principle target for a protective neutralizing antibody response. Through stabilization of the pre-fusion form, the molecular clamp promotes the production of highly neutralizing and broadly cross-reactive antibodies.

Product Characteristics

MCT technology enables rapidly generate novel subunit vaccines purely from sequence information.

Subunit vaccines

- **Advantages** include:
  - Subunit vaccines are safe and economical technology compared to live-attenuated pathogens or inactivated toxins
  - Production is relatively inexpensive due to the ease of production and simplistic composition
- **Limitations** include:
  - Relatively decreased immunity, potentially requiring the addition of immunostimulatory agents (adjuvants)

Current Status

UQ's COVID-19 subunit vaccine is not approved anywhere for use.

Subunit vaccine have been popular approaches in the development of MERS vaccine, mostly focusing on the recombinant receptor binding domain (RBD) of the S protein produced in heterologous expression systems. However, subunit vaccines are often administered along with adjuvants to boost the immunogenicity of the recombinant antigens. Subunit vaccines for MERS have been assessed in preclinical animal studies.

Subunit vaccines have been extensively evaluated for coronaviruses and are safe vaccine platforms, and thus have considerable potential to be applied for COVID-19.

COVID-19 Status

On January 24 2020 the University of Queensland announced its COVID-19 vaccine project based on its MCT technology, in collaboration with CEPI.

On February 23 2020 UQ announced their first vaccine candidate had met an early proof-of-concept milestone and would undergo further testing in advance of formal pre-clinical studies, with the aim to enter investigational clinical testing in mid-2020.

UQ's COVID-19 subunit vaccine is not currently being evaluated in any clinical trials.

Source: Guggenheim Securities LLC Research

Subunit Vaccines Relevant Preclinical Data Summary

Several promising subunit vaccines against MERS-CoV have been developed and assessed in preclinical studies.

MERS-CoV subunit vaccines based on the S1 domain typically require the use of adjuvant or fusion with an immune enhancer to heighten immunogenicity. Several studies have indicated that RBD fused with Fc fragment of human IgG (RBD-Fc) elicited strong systemic neutralizing antibody and cellular immune responses in vaccinated mice.

MERS antigen	ROA	Results	Reference
MERS-CoV S1 protein	SC	Adjuvanted (MF59) MERS-CoV S1 protein protected hDPP4 transgenic mice against lethal MERS-CoV challenge, where the protection correlated well with the neutralizing antibody titer.	Wang et al., 2017c
MERS-CoV S1 protein	IM	Immunization with adjuvanated (Advax HCXL adjuvant and Sigma Adjuvant System) S1 protein reduced and delayed virus shedding in the upper respiratory tract of dromedary camels and provided complete protection in alpaca against MERS-CoV challenge.	Adney et al., 2019
MERS-CoV S protein trimer on Fd	IM	Recombinant prefusion trimeric MERS-CoV S protein induced high titer of neutralizing antibodies in BALB/cJ mice.	Pallesen et al., 2017
RBD trimer on Fd	SC or IM	Adjuvanted (alum) RBD-Fd induced neutralizing antibodies in BALB/c mice and protected (83%) hDPP4 transgenic mice against lethal MERS-CoV challenge.	Tai et al., 2016
RBD fused to Fc	SC	Adjuvanted RBD-Fc induced high titer of neutralizing antibodies in BALB/c mice and New Zealand white rabbits.	Ma et al., 2014b
RBD fused to Fc	SC	Mice immunized with the vaccine and Montanide ISA 51 adjuvant produced neutralizing antibodies which inhibited binding of the RBD to DPP4 receptor, neutralizing MERS-CoV infection.	Du et al., 2013
RBD fused to Fc	IN or SC	Mice vaccinated with both immunization routes in the presence of adjuvants (Montanide ISA 51 adjuvant for SC and Poly(I:C) for IN) elicited systemic humoral immune responses. Stronger systemic cellular immune responses and local mucosal immune responses were observed in mice immunized via IN route.	Ma et al., 2014a
RBD fused to Fc	IM	hCD26/DPP4 transgenic mice immunized with the vaccine in the presence of adjuvant, AddaVax elicited neutralizing antibodies and were protected against MERS-CoV infection.	Nyon et al., 2018
RBD fused to Fc	SC	Mice immunized with the vaccine alone produced detectable neutralizing antibodies and cellular immune responses. Immunogenicity of the vaccine improved when the adjuvants such as Freund's adjuvant, alum, monophosphoryl lipid A, Montanide ISA51 or MF59 was included in the formulation. MF59 was demonstrated to be superior in enhancing the vaccine immunogenicity and protection against viral challenge.	Zhang et al., 2016
Recombinant RBD	IM or SC	When the subunit vaccine was administered together with combination of alum and CpG ODN, optimized RBD-specific humoral and cellular immunity were elicted. Robust RBD-specific antibody and T-cell responses were induced in mice immunized with the vaccine in combination with IFA and CpG ODN, but low level of neutralizing antibodies were induced.	Lan et al., 2014
Recombinant RBD	IM	Rhesus macaques immunized with the subunit vaccine and alum adjuvant produced neutralizing antibodies and experienced mitigated clinical symptoms when challenged with MERS-CoV.	Lan et al., 2015
rNTD of S protein	IM	Immunization with rNTD of MERS-CoV S protein adjuvanted with alum induced neutralizing antibodies and reduced the respiratory tract pathology of BALB/c mice challenged with MERS-CoV.	Jiaming et al., 2017

Source: Yong et al Front Microbiol 2019, Guggenheim Securities LLC Research

SARS CoV-2 Spike Protein Vaccine – NVAX

Background and Mechanism

Novavax's vaccine candidates were derived from the coronavirus spike (S) protein and will utilize Matrix-M, a saponin-based adjuvant to boost immune responses by stimulating entry of APCs into the injection site and enhancing presentation in local lymph nodes.

Novavax initiated efforts in January to develop a novel vaccine to protect against COVID-19 in animal model (mice and non-human primates), with the goal of moving one or more optimized COVID-19 candidates (high affinity and neutralizing antibodies) into human clinical trials. The candidates were created with its proprietary recombinant protein nanoparticle technology platform to generate antigens derived from the coronavirus spike (S) protein, which the company has expressed stably in a baculovirus system. Novavax has previous experience developing vaccines against previous coronaviruses, including MERS and SARs, where they showed strong immunogenicity and protection in preclinical testing.

Product Characteristics

- Nanoparticle vaccine with full length recombinant S trimers and Matrix-M adjuvant
- Nanoparticle discovery platform used in non-coronavirus candidates RSV, CCHF, HPV, VZV, EBOV
- Engineered from the genetic sequence of COVID-19 virus and binds efficiently with the same human receptors targeted by the virus

Current Status

Currently Novavax's preclinical vaccine candidate is not approved for use in any indication or location.

COVID-19 Status

The company expects COVID-19 phase 1 clinical trials in healthy adults to initiate in May-June 2020, with data expected in the summer. The phase 1 trial will enroll healthy adults and consist of both an adjuvant and adjuvant-sparing arm to demonstrate strong immunogenicity, determine the importance of the adjuvant, and measure the induced anti-spike IgG.

In early March the Coalition for Epidemic Preparedness Innovations (CEPI) awarded an initial funding of $4M to support development and is in ongoing discussions to address additional funding costs through phase 1. Additionally, Novavax and Emergent BioSolutions (EBS) announced an agreement March 10th whereby EBS will utilize its molecule-to-market contract development and manufacturing (CDMO) services to support the vaccine candidate's progression into the clinic. EBS will mobilize both its developmental and manufacturing services to supply both drug substance and drug product.

Source: Company reports, Guggenheim Securities

Oral Prophylactic COVID-19 Vaccine – VXRT

Background and Mechanism

Vaxart's recombinant vaccine candidate is based on its oral Vector-adjuvant platform (VAAST) and uses an adenovirus type 5 (Ad5) non-replicating vector to carry genes coding for an antigen and an adjuvant to the mucosa of the small intestine.

Vaxart initiated a program in late January to develop a coronavirus vaccine and intends to generate vaccine candidates based on the published genome of SARS-CoV-2 and evaluate them in preclinical models for their ability to generate both mucosal and systemic immune responses. Unlike injectable vaccines that protect through systemic immunity, Vaxart's oral vaccines (including H1 influenza tablet) have been shown to protect against respiratory infection based on mucosal immunity, which is of particular interest since the coronavirus is primarily an infection of the respiratory tract.

Product Characteristics

- Room temperature-stable oral tablet
- Targeting mucosal and systemic immune responses

Current Status

Currently Vaxart's preclinical vaccine candidate is not approved for use in any indication or location.

COVID-19 Status

Phase 1 clinical study anticipated to begin in early 2H20.

In January, Vaxart initiated a program to develop a coronavirus vaccine candidate and is currently producing multiple research grade candidates to be evaluated in a preclinical model. On March 18th, Vaxart announced an agreement with Emergent BioSolutions (EBS) allowing the company to leverage EBS' CDMO services immediately and upon Vaxart's election, produce bulk cGMP vaccine for the phase 1 clinical study. In the meantime, the company has placed all HPV development on hold in order to focus its efforts on the COVID-19 vaccine. The CEO has stated that external funding or collaboration will be needed to bring its vaccine past preclinical studies.

Source: Company reports, Guggenheim Securities

COVID19 Vaccine – JNJ

Background and Mechanism

JNJ is currently expanding a partnership with the biomedical advanced research and development authority (BARDA) in order to create a vaccine against COVID-19 and screen an existing library to antiviral compounds for those with activity against COVID-19. The vaccine will be developed with the same AdVac and PER.C6 systems that were also used to develop the company's Ebola vaccine.

Current Status / Commentary

JNJ hopes to have a vaccine candidate ready by the end of March 2020, and hopes to begin human clinical trials in early November. The company is actively engaged in developing new vaccines across multiple types of infectious disease with pandemic potential (hepatitis, TB, influenza, HIV, Zika, and Ebola), thus have a relatively robust capacity to discover, evaluate, and manufacture these compounds.

Product Characteristics

While there is no clinical candidate yet selected (that has been made public), we know that the company intends to use their AdVac adenovirus vector development system and PER.C6 manufacturing system to develop the vaccine, which tare the same systems they have used to rapidly produce an Ebola vaccine that is currently being trialed in Africa.

COVID-19 Status

The company hopes to have a candidate by the end of March 2020, and begin human clinical trials in early November 2020.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Vaccine Development – SAN-PAR

Background and Mechanism

Sanofi Pasteur, the Vaccines Global Business Unit of Sanofi (SAN-PAR) is currently working to develop a SARS-CoV-2 vaccine. The ongoing CoV-2 development work is being done in collaboration with the Biomedical Advanced Research and Development Authority (BARDA).

The company is leveraging its prior experience with SARS-CoV via its 2017 acquisition of Protein Sciences and its recombinant DNA platform. In preclinical studies, the company's original SARS-CoV vaccine candidate was immunogenic and afforded partial protection as assessed in animal challenge models.

From a production perspective, the vaccine candidate will leverage SNY-PARs baculovirus expression platform, from which of SAN's currently approved recombinant influenza product Is derived. Since there is already a licensed vaccine based on this platform, research and materials should be produced relatively quickly for clinical testing.

On February 18th, 2020

*"In addition to Kevzara, **Sanofi Pasteur**, the vaccines global business unit of Sanofi, is leveraging previous development work for a SARS vaccine as part of our goal to quickly develop a COVID-19 vaccine."*

- John Reed, M.D., Ph.D., Sanofi's Global Head of Research and Development

Sources: UpToDate; AdisInsight; SAN-PAR Press Release and Filings

Vaxil's Signal Peptide Vaccine

Background and Mechanism

Signal peptide domains are short ~13–50 amino acid-long lipophilic targeting sequences, typically located at the N-terminus of proteins destined for secretion or for integration within cellular membranes. SPs have been found to have high antigen specific sequence variability that can enable, inhibit or activate innate (NK via ADCC), and adoptive (T-cell- and antibody-mediated) immunity.

SP vaccines have been found to generated combined and diversified antigen-specific CD4+/CD8+ T-cell and B-cell immunity irrespective of HLA repertoire.

Current Status

Signal peptide vaccines are in preclinical and clinical development, and are currently not licensed for any indication.

Initial clinical experience using Vaxil's ImMucin, a MUC1 TAA entire SP domain-based therapeutic vaccine, in patients with MUC1-positive tumors further validated the pre-clinically observed robust and diversified T/B-cell immunological responses.

Signal peptide vaccines have not been evaluated for any coronaviruses in preclinical or clinical studies.

Product Characteristics

Proposed advantages of synthetic signal peptide vaccines:

- Induction of a highly specific response, with limited short-term toxicity
- Chemical stability and absence of pathogens and other contaminating mammalian substances
- Cost effective production

Potential limitations:

- Relatively unproven vaccine platform for coronaviruses compared to other approaches in preclinical and clinical development

COVID-19 Status

On February 14 2020 Vaxil announced the design of its preliminary vaccine candidate based on successful in vivo experiments testing a tuberculosis signal peptide vaccine. On March 10 Vaxil submitted a new patent application for its anti-infective vaccines platform.

In Q2 2020, Vaxil plans to initiate non-GMP manufacturing and make the non-GMP product available for pre-clinical testing. In addition, Vaxil plans to explore partnerships and other possibilities to test the vaccine.

Vaxil's signal peptide vaccine is not currently being evaluated in any clinical trials.

Source: Company reports, Guggenheim Securities LLC Research

COVID-19 vaccine – ExpreS^{2}ion Biotechnologies

Background and Mechanism

ExpreS^{2}ion's proprietary technology platform, ExpreS2, is a non-viral insect cell expression system that quickly establishes stable polyclonal pools that provide high protein expression levels without selection pressure. Compared with the traditional baculovirus system, the Drosophila S2 insect cell expression system (ExpreS2) has several advantages, including: a more homogeneous glycosylation profile; better reproducibility between manufacturing runs; several options for cultivation modes, such as perfusion that allows for long cultivation times with daily harvests; no cell lysis, resulting in lower levels of contaminating host cell proteins.

Current Status / Commentary

Currently ExpreS^{2}ion's COVID-19 is not approved anywhere for any use.

Product Characteristics

- **Vaccine**

COVID-19 Status

On Feb. 6th, 2020, ExpreS^{2}ion has announced initiating a vaccine development program against COVID-19. ExpreS^{2}ion will apply its clinically validated Drosophila S2 insect cell expression system, ExpreS2, to produce 2019-nCoV viral antigens in the company's clinically validated cell lines, as well as in ExpreS2ion's new HighMan-S2™ immunogenicity-enhancing cell line.

On March 6th, ExpreS^{2}ion (as part of a consortium) was awarded an EU Horizon 2020 grant for the COVID-19 (SARS-CoV-2) Coronavirus vaccine development program. The aim of the grant is to support the consortium in development of a COVID-19 vaccine candidate, including performing a Phase I/IIa clinical trial. The aim is to initiate clinical investigations within 12 months.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

INO-4800 – INO

Background and Mechanism

INO-4800 is a DNA vaccine matched against the novel coronavirus SARS-CoV-2. Using Inovio's (INO) proprietary hand-held CELLECTRA platform, this therapeutic delivers DNA plasmids into host cells designed to trigger expression of proteins to generate T-cell and antibody responses. CELLECTRA is a handheld, AA battery-powered intradermal drug delivery system that uses electroporation to open the cells to receive the DNA plasmids.

INO's R&D platform is broadly focused on immunotherapy for the treatment of cancer and infectious diseases. Its pipeline includes a clinical-stage Zika vaccine (INO-A002), MERS vaccine (INO-4700), Ebola vaccine (INO-4201)

Current Status / Commentary

INO-4800 is currently in preclinical stages of development and expects to enter clinical trials in April 2020

Product Characteristics

- **Transdermal injection with a AA battery handheld device**.
- **INO expects ~1 million doses available by YE 2020.**

COVID-19 Status

Company expects to enter the clinic April 2020 with data in Fall 2020 and ~1 million doses available by YE 2020

Source: Guggenheim Securities LLC Research; clinicaltrials.org

TNX-1800 – TNXP

Background and Mechanism

TNX-1800 is a live, modified horsepox virus designed to express the SARS-CoV-2 spike protein. The company had recently highlighted potential advances of horsepox over vaccinia including strong immunogenicity with potentially improved tolerability, and replication in human cells that could provide direct antigen presentation via Class I MHCs.

Current Status / Commentary

TNX-1800 is currently in the R&D stages of development in collaboration with Southern Research.

TNXP on March 20th, 2020 presented to the World Health Organization preliminary background information on the potential for horsepox viruses to be re-purposed as a SARS-CoV-2 vaccine (link)

Product Characteristics

- **Percutaneous injection**

COVID-19 Status

Under early development in collaboration with Southern Research

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Takis Biotech/Evvivax vaccine

Background and Mechanism

Takis and Evvivax are working on a DNA vaccine against COVID-19. This vaccination approach requires only knowing the underlying viral genome (RNAnome?) in order to synthesize sequence expressing the particular pathogenic protein that is desired to have a patient mount an immune response against. These sequences can then be injected and synthesized, resulting in the production of pathogenic protein, and can cause a concomitant immune response

Current Status / Commentary

- Advantages of DNA vaccines are that they can be faster to produce, and have zero potential for infection or disease in a treated patient.
- Disadvantages of DNA vaccines are that they can be tough to find an appropriate target to express, that will be properly folded to generate the proper immune response against the full wild-type pathogen.
- Management claims they have generated dozens of antibodies capable of neutralizing viruses and pathogenic bacteria with this approach.

Product Characteristics

We know of no product candidate yet, but as a DNA vaccine this would likely be nucleic acid sequenced packaged in a viral vector that would be injected into patients.

COVID-19 Status

Takis and Evvivax are working on this vaccine, though no additional updates have been made.

Source: Company reports, Guggenheim Securities LLC Research

Adenoviral vaccine – CanSino Biologics

Background and Mechanism

CanSino and China's Academy of Military Medical Sciences are collaborating to develop an adenoviral vector-based vaccine. The vaccine utilizes an engineered replication defective Adenovirus Type 5 vector (Ad5) to express the SARS-COV2 spike protein.

CanSino previously developed an adenovirus-based Ebola vaccine, which received approval by the CFDA in 2017. The Ad5-EBOV vaccine was evaluated in a Phase 2 study in 500 patients in Sierra Leone. The study compared 2 doses of Ad5-EBOV (8e10 viral particles or 1.6e11 viral particles) to placebo. Results published in Lancet (2016) showed that Ad5-EBOV led to high humoral immune response that peaked at 4 weeks that declined by ~85% by 6 months post-injection, suggesting the need for booster doses. The 8e10 dose was determined to be the optimal dose. Most AEs were mild or moderate.

Product Characteristics

- **I.M. injection**
- **Adenovirus-based vaccine can present pre-existing immunity.** Ad5-based vaccines have been shown to have high levels of pre-existing antibodies.
- **Additional details around the program have not been disclosed, to our knowledge.**
- **The company previously reported in 2017 it's 700,000 sq ft, 70-million-dose-capacity manufacturing site, which the company said is cGMP-compliant.**

Current Status / Commentary

CanSino received approval for a clinical trial on March 18th and the study design of its Phase 1 trial has been posted on clinicaltrials.gov and ChiCTR.

COVID-19 Status

The company plans to conduct a Phase 1 study in 108 healthy adults to evaluate 3 different dose cohorts (NCT04313127, ChiCTR2000030906). CanSino filed an pre-IND review application on March 17th and received approval for a clinical trial on March 18th.

According to the company, preclinical studies showed that the vaccine induced a strong immune response.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

CDX-CoV – Codagenix/Serum Institute of India

Background and Mechanism

Codagenix developed a platform to design live-attenuated virus using a computer algorithnm, which could significantly accelerate the development compared to traditional approach.

Viral genomes are processed by Codagenix's computer-based algorithm to introduce hundreds of silent mutations into the genome to use codon pairs that are underrepresented in human cells. The resulting genome that is "de-optimized" for translation in the human host cell is then synthesized, assembled into a whole genome, transfected into cells and live, "de-optimized", attenuated viruses are recovered. This rapid, cell-culture based process can generate lead vaccine candidates ready for animal studies in weeks as compared to months, for traditional approaches to attenuating live viruses.

Current Status / Commentary

- Project initiated Feb 13th, 2020, in collaboration with the Serum Institute of India.
- Currently in "discovery" stage.

Product Characteristics

- **Algorithm-based vaccine design,** taking less than 2 months from disease outbreak to clinical lot manufacturing.

COVID-19 Status

- Codagenix has designed multiple nCoV vaccine candidate genomes using its proprietary deoptimization technology. The vaccine viruses will then be grown and tested in vivo by contracted laboratories suitable for containment, prior to testing in clinical trials.
- The Serum Institute of India, a vaccine manufacturer and distributor with a global footprint, will then scale-up the manufacture of the vaccine to ensure its availability to meet a critical public health need.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Adenoviral NasoVAX vaccine – Altimmune

Background and Mechanism

Altimmune is developing an adenovirus-based NasoVAX vaccine for COVID-19. The vaccine utilizes an replication deficient Ad5 vector to express the SARS-COV2 spike protein with a CMV promoter.

ALT is also developing its NasoVax-based vaccine for influenza. Phase 2a results showed 100% seroprotection with single intranasal dose (at 2 of the 3 doses tolerated) that was durable at least 1 year after a single dose. NasoVax was safe and well tolerated at all doses tested.

Current Status / Commentary

The program is currently in preclinical development.

Product Characteristics

- **Intranasal administration.**
- **Adenovirus-based vaccine can present pre-existing immunity.** Ad5-based vaccines have been shown to have high levels of pre-existing antibodies.
- **Additional details around the program have not been disclosed, to our knowledge.**
- **ALT has noted that its manufacturing is "quickly scalable to millions of doses".**
- **The product can be stored at room temperature.**

COVID-19 Status

Altimmune has completed the design and synthesis of the vaccine and is now advancing the program toward manufacturing and preclinical animal testing. Currently underway is expansion of seed material for manufacturing and immunogenicity studies in animals.

The company expects to begin a Phase 1 study in 3Q20 with topline readout in 4Q20. It also expects to begin GMP manufacturing by mid-year.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

Adenoviral vaccine – Greffex

Background and Mechanism

Greffex is developing an adenovirus-based NasoVAX vaccine for COVID-19. The vaccine utilizes a genetically engineered adenovirus-based vector. Greffex notes that its adenovirus platform are fully deleted and helper virus-independent.

Current Status / Commentary

The program is currently in preclinical development.

Product Characteristics

- **Adenovirus-based vaccine can present pre-existing immunity.** Ad5-based vaccines have been shown to have high levels of pre-existing antibodies.
- **Additional details around the program have not been disclosed, to our knowledge.**
- **Greffex has committed to distributing the vaccine to other countries for free.**

COVID-19 Status

Greffex has completed the design of its vaccine and is advancing its program towards preclinical testing.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

DNA & Measles-Based Vaccine – Cadila Healthcare (532321-IN)

Background and Mechanism

Zydus Cadila is launching a two-pronged research effort against COVID-19 – a DNA-based vaccine and a live attenuated measles virus.

Current Status / Commentary

Both programs are currently in the R&D stages of development with teams at the Vaccine Technology Center in India and another team at Etna Biotech in Italy.

Product Characteristics

- **Unknown**

COVID-19 Status

Under early development

Source: Guggenheim Securities LLC Research; clinicaltrials.org

COVID-19 S-Trimer – GSK

Background and Mechanism

S-Trimer is a trimeric SARS-CoV-2 spike (S)-protein subunit vaccine candidate.

S-Trimer is designed to resemble the native S (spike) protein and is produced via a rapid mammalian cell-culture based expression system. It will be combined with GSK's AS03 adjuvant system.

It is currently in preclinical stages.

Sources: UpToDate; AdisInsight; Clover Biopharma Press Release; Company Website

Antibodies for the treatment of COVID-19

1. Convalescent serum / plasma derived antibody therapy
2. Recombinant antibody / protein therapy

Inactivated Plasma Therapy

Background and Mechanism

Patients with resolved viral infection will develop a polyclonal antibody immune response to different viral antigens of COVID-19. Some of these polyclonal antibodies will likely neutralize the virus and prevent new rounds of infection.

For **inactivated plasma therapy**, patients with resolved cases of COVID-19 can donate plasma, which is then transfused into infected patients. **Convalescent plasma** or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone.

Product Characteristics

Blood is drawn and screened from individuals who have been infected with COVID-19 and recovered, and subsequently transfused into infected or high-risk patients.

- **Advantages** include:
  - Well established procedure and rationale with historical evidence of protective efficacy against infectious diseases
- **Limitations** include:
  - More effective when used for prophylaxis than for treatment of disease
  - Known risks include inadvertent infection with another agent or immunological reactions

Current Status

Plasma donation is a well established procedure, and transfusion of plasma is routine medical care. Passive administration of convalescent antibodies has extensive clinical evidence of providing immunity to susceptible individuals, including against SARS-CoV, MERS-CoV, and H1N1 influenza.

A similar rationale was used in the treatment of several Ebola patients with convalescent serum during the outbreak in 2014–2015, including two American healthcare workers who became infected. A protocol for the use of convalescent plasma in the treatment of Middle East respiratory syndrome coronavirus was established in 2015.

The efficacy of this therapy for COVID-19 cannot be inferred without carrying out a controlled clinical trial, but it remains a promising approach, in our view.

COVID-19 Status

As the outbreak continues, more patients who survived infection may become available to serve as donors to make antisera for COVID-19, and a sizeable stock could be developed to serve as a treatment for the sickest patients.

Reports from China have shown that out of 245 COVID-19 patients offered convalescent plasma therapy, 91 cases showed improvement in clinical indicators and symptoms.

Inactivated plasma therapy is currently being evaluated in 2 clinical trials.

Source: Guggenheim Securities LLC Research

Inactivated Plasma Relevant Clinical Data

Convalescent sera has been used to stem viral outbreaks from diseases such as measles, mumps, and influenza, including the 1918 influenza virus pandemic. For the two most relevant coronavirus outbreaks, SARS1 in 2003 and MERS in 2012, convalescent serum was used in both situations with evidence of safety and efficacy in reducing viral load.

Historical use of convalescent serum during viral epidemics:

- In the 2009–2010 **H1N1** influenza virus pandemic, convalescent serum antibody preparations obtained by blood plasma withdrawal were used to treat individuals with severe H1N1 2009 infection requiring intensive care. Serum-treated individuals showed reduced respiratory viral burden, serum cytokine responses, and mortality (absolute risk differences in mortality between the treatment and control groups was 8% to 26%, respectively, with a pooled risk difference of 21%) (link)
- Convalescent serum was used in the 2013 West African **Ebola** epidemic, and a small nonrandomized study in Sierra Leone revealed significantly longer survival for those treated with convalescent whole blood relative to those who received standard treatment (link)

Use of convalescent serum for coronaviruses:

- In a study of 80 patients with **SARS** infections in Hong Kong, patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the need for earlier administration for better outcomes (link)
- Three patients with **SARS** in Taiwan were treated with 500 mL convalescent serum, resulting in a reduction in serum virus titer; each patient survived (link)
- Analysis of 99 samples of convalescent sera from patients with **SARS** showed that 87 had neutralizing antibody, with a geometric mean titer of 1:61. This suggests that antibody declines with time and/or that few patients make high-titer responses, and that non-neutralizing antibodies may be produced that contribute to protection and recovery, as described for other viral diseases (link)

Source: Casadevall and Pirofski JCI 2020, Guggenheim Securities LLC Research

Inactivated Plasma Ongoing Clinical Trials (Global)

Inactivated plasma is currently being evaluated in 2 trials globally for treatment of COVID-19

NCT ID / trial link	Title	Enrollment	Sponsor	Geography	Primary Est. Completion
ChiCTR2000030010	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	N=100	Wuhan Jinyintan Hospital	China	05/31/2020
NCT04292340	The Efficacy and Safety of Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of Novel Coronavirus Pneumonia Patient (COVID-19) : An Observational Study	N=15	Shanghai Public Health Clinical Center	China	07/31/2020

Source: clinicaltrials.gov, Guggenheim Securities LLC Research

IVIg

Background and Mechanism

Intravenous immunoglobulins (IVIg) is the pooled antibody fractions from many different blood donors. IVIg is primarily composed of IgG, with only small amounts of IgM and IgA present. This treatment is used to treat a variety of autoimmune diseases as well as to treat immunocompromised patients. In autoimmune diseases, the large bolus of IgG can help to prevent the recycling of autoantibodies by swamping out the FcRn recycling system. For immunocompromised patients, the large infusion of IgGs can replace missing endogenous antibodies, providing these patients with the humoral immunity they are lacking. In COVID-19, patients who have recovered from disease will have developed effective neutralizing antibodies towards COVID-19, and the goal is to harvest these patients' IgG and use as an infusible immunotherapy.

Current Status / Commentary

- This approach is similar to that used by Takeda in their TAK-888 drug (more on this in next section).
- We believe this approach has merit, but is by definition a lagging therapy as it requires a sufficiently large number of patients to have known COVID-19 infection and recovery to harvest enough plasma to create the product. On account of these limitations, we would expect this approach to be unlikely to ever reach mainstream treatment status, and more importantly, in our view, if monoclonal cocktails against COVID-19 capsid antigens are produced, this product would likely have very little commercial potential.

Product Characteristics

This would be an infusible, human product. It is, in effect, the provision of a polyclonal IgG fraction that should contain multiple neutralizing antibodies against COVID-19.

COVID-19 Status

There are two planned trials for IVIg for COVID-19:

NCT04264858 is a 10-patient placebo-controlled, open-label study evaluating IVIg vs. g-globulin in patients diagnosed with acute severe 2019-nCoV pneumonia. The study's **primary endpoint** is time to clinical improvement (up to 28 days). The study has a planned March 2020 start date and is expected to complete by the April/May 2020 timeframe.

NCT04261426 is an 80 patient placebo-controlled, open-label study evaluating IVIg vs. "standard care" in adults with lab confirmed 2019-nCoV infection. The study's **primary endpoint** is clinical improvement (based on a 7-point scale) and improvement in lung injury score. The sponsors estimate the study will complete in the May/June 2020 timeframe.

Source: Guggenheim Securities LLC Research

TAK-888 – Takeda (4502-TKS)

Background and Mechanism

TAK-888 is a anti-SARS-CoV-2 polyclonal serum to treat high-risk individuals with COVID-19. This requires access to source plasma from people who have successfully recovered from COVID-19 or who have been vaccinated, once a vaccine is developed. Hyperimmune globulins are plasma derived-therapies that have previously been shown to be effective in the treatment of severe acute viral respiratory infections and may be a treatment option for COVID-19. H-IG works by concentrating the pathogen-specific antibodies from plasma collected from recovered patients or vaccinated donors in the future. By transferring the antibodies to a new patient, it may help that person's immune system respond to the infection and increase their chance of recovery. This is a very similar approach to the IVIg approach mentioned previously.

Current Status / Commentary

- This approach has merit, but is by definition a lagging therapy, as it requires a sufficiently large number of patients to have known COVID-19 infection and recovery to harvest enough plasma to create the product. On account of these limitations, we would expect this approach to be unlikely to ever reach mainstream treatment status, and more importantly, in our view, if monoclonal cocktails against COVID-19 capsid antigens are produced, this product would likely have very little commercial potential.
- The company is also studying whether Takeda's currently marketed and pipeline products may be effective treatments for infected patients

Product Characteristics

- Because the plasma needed for TAK-888 is unlikely to come from current plasma donors, Takeda will initially produce the therapy in a segregated area within its manufacturing facility in Georgia, and development and production of it should not negatively impact Takeda's ability to produce its other plasma-derived therapies.
- This would be an infusible human product. It is, in effect, the provision of a polyclonal IgG fraction that should contain multiple neutralizing antibodies against COVID-19.

COVID-19 Status

The current TAK-888 status is not known at this time.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

COVID-HIG – EBS

Background and Mechanism

COVID-HIG is a plasma-based product candidate manufactured from human plasma with antibodies to COVID-19 being developed as potential treatment for severe hospitalized patients and protection for at-risk individuals.

COVID-HIG is being developed on EBS' hyperimmune platform that has a well-established safety database and several FDA approved products including VIGIV (smallpox [human]), BAT (botulism [equine]), and Anthrasil (anthrax [human]). Hyperimmunes are polyclonal antibody therapeutics derived from plasma that leverage the immune response in humans or animals and can provide immediate protection from infection.

Current Status

Currently EBS' preclinical therapeutic candidate is not approved for use in any indication or location.

Product Characteristics

- Human polyclonal hyperimmune
- Immediate protection from infection

COVID-19 Status

EBS anticipates beginning a clinical study as early as 3Q20.

Using existing infrastructure and capabilities deployed for a recent phase 2 trial in Influenza A, EBS has initiated plasma collection efforts with a goal of manufacturing clinical material within the next four to five months.

Source: Company reports, Guggenheim Securities LLC Research

COVID-EIG – EBS

Background and Mechanism

COVID-EIG is a plasma-based product candidate manufactured from immunized horse plasma with antibodies to COVID-19 being developed as potential treatment for severe hospitalized patients.

COVID-EIG is being developed on EBS' hyperimmune platform that has a well-established safety database and several FDA approved products including VIGIV (smallpox [human]), BAT (botulism [equine]), and Anthrasil (anthrax [human]). Hyperimmunes are polyclonal antibody therapeutics derived from plasma that leverage the immune response in humans or animals and can provide immediate protection from infection.

Current Status

Currently EBS' preclinical therapeutic candidate is not approved for use in any indication or location.

Product Characteristics

- Equine-derived polyclonal hyperimmune
- Immediate protection from infection

COVID-19 Status

EBS anticipates beginning a clinical study as early as 3Q20.

Using existing infrastructure and capabilities deployed for a recent phase 2 trial in Influenza A, EBS has initiated plasma collection efforts with a goal of manufacturing clinical material within the next four to five months.

Source: Company reports, Guggenheim Securities LLC Research

Anti-Corona IgG – KMDA

Background and Mechanism

Anti-Corona polyclonal IgG is produced from plasma derived from healthy donors that have recovered from COVID-19, which will be purified to collect antibodies to the novel virus.

KMDA plans to utilize its Hyper-Immunoglobulin (IgG) Platform Technology to develop Anti-Corona (COVID-19) Immunoglobulin as a potential therapy for severely ill coronavirus patients. This kind of treatment is also known as a "passive vaccine" as it provides antibodies to fight the virus rather than relying solely on the immune system of the infected person.

Current Status

Currently KMDA's preclinical therapeutic candidate is not approved for use in any indication or location.

Product Characteristics

- Human-derived polyclonal immunoglobulin
- Immediate protection from infection

COVID-19 Status

KMDA has emphasized that the development plan and manufacturing of Anti-Corona IgG are highly dependent on (1) the availability of hyper-immune plasma, (2) the level of antibodies in recovered patients (2) the regulatory path set forth by health authorities.

The plan to initiate development of the therapeutic was announced on March 11th and the company has advised that they have been working with Israeli regulatory authorities and local medical institutions (including Sheba Medical Center) to advance the program. KMDA anticipates that they it have the product ready for compassionate treatment in a matter of months.

Source: Company reports, Guggenheim Securities LLC Research

Anti-COVID-19 Antibody Cocktail – REGN

Background and Mechanism

REGN is using its velocimmune platform (mouse with human immune system) to develop fully human antibodies against COVID-19. The end goal is to create a cocktail containing two high-affinity antibodies against different COVID-19 capsid epitopes. An antibody produced against these targets would likely **(1)** prevent the virus from being able to enter cells and replicate, and **(2)** would mark the virus for phagocytosis by Fc gamma receptors by macrophages and other phagocytes.

Current Status / Commentary

We believe this is a sound approach for three reasons; (1) having a therapeutic antibody (or antibody cocktail) on hand could provide both rapid treatment potential to infected patients, and a strong prophylactic treatment to high-risk patients, (2) by using a cocktail against two epitopes instead of one the company is able to target multiple viral variants and should hopefully prevent the virus from mutating away from a single targeted epitope, and (3) REGN has an excellent antibody generation engine and has a track record of successful antibody generation.

Product Characteristics

While no product has yet been made public, as an antibody therapy this cocktail would either be infused or injected subQ. Our best guess would be that patients suffering acute infection would receive the drug IV, as a much larger bolus could be needed, whereas those getting it prophylactically could possibly use a smaller subQ dose.

COVID-19 Status

- Regeneron has identified hundreds of virus-neutralizing antibodies; the goal is to select its top two antibodies and initiate large-scale manufacturing by mid-April with antibody cocktail therapy.
- Potential to enter human clinical studies by early summer.
- The company plans to scale up production to 200,000 preventative doses or approximately 20,000 treatment doses per month by the end of August.

Source: Company reports, Guggenheim Securities LLC Research

Antibody Therapeutic – LLY and AbCellera

Background and Mechanism

LLY and AbCellera are co-developing an anti-COVID19 antibody therapeutic. We would expect this antibody would be raised against 1 or more COVID19 capsid antigens. An antibody produced against one of these targets would likely **(1)** prevent the virus from being able to enter cells and replicate, and **(2)** would mark the virus for phagocytosis by Fc gamma receptors by macrophages and other phagocytes.

Current Status / Commentary

- The collaboration will leverage AbCellera's rapid pandemic response platform, and Lilly's global capabilities for rapid development, manufacturing and distribution of therapeutic antibodies.
- Abcellera received blood samples from a COVID-19 recovered patient and screened 5 million immune cells to discover potentially neutralizing antibodies. This resulted in >500 unique fully human sequences

Product Characteristics

- While no product yet exists, an anti-COVID19 antibody could be helpful in treating acute infection as well as in prophylactic use in high-risk patients.
- As an antibody, this therapeutic would either be infused or subQ injected, and would likely have a ~3w half-life in circulation (assuming no half-life extending modifications were engineered into the Fc backbone).

COVID-19 Status

The next step is to screen the identified antibodies to find the ones most effective in neutralizing SARS-CoV-2.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Bevacizumab (Avastin)

Background and Mechanism

Avastin is a humanized VEGF-A antibody that is currently approved to treat multiple types of cancer as well as off-label use in wet age-related macular degeneration (wet AMD). VEGF-A is the dominant growth factor for blood vessel growth (angiogenesis and vasculogenesis). Multiple studies have established a role for VEGF as potential therapeutic target in acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) due to increased vascular permeability and induced pulmonary edema. In addition, recent evidence has revealed higher VEGF levels in COVID-19 patients compared with healthy controls. The rise of VEGF levels may be caused by hypoxia, severe inflammation, and upregulation of the infected respiratory tract epithelium itself. Use of Avastin in these patients could reduce the VEGF levels, and in turn potentially reduce the pulmonary edema suffered by the most severe patients.

Product Characteristics

Avastin has been approved and used for years. It is given IV (or intravitreally in the case of wet AMD), in clinical trials, and the drug's most common adverse reactions incidence (incidence > 10%) were epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. The key warnings that would likely be most applicable to COVID-19 patients in ARDS would be a warning for grade 3/4 hemorrhage, and a warning for hypertension and bp monitoring.

Current Status / Commentary

- In February 2020 a novel coronavirus pneumonia trial was conducted in 11 patients with severe and severe new crown pneumonia. It suggested that Avastin plus conventional therapy was effective in treating dyspnea symptoms in patients with new coronary artery pneumonia, and no obvious adverse reactions were observed.
- While Avastin specifically (and VEGF inhibitors generally) could potentially reduce some of the damage associated with ARDS from COVID-19, in our view, the mechanistic rationale here is weaker than for some of the other treatments under development.
- NCT04305106 is using an odd trial design that is double blinding the study but using a "no intervention" control vs. a placebo. Blinding in this situation seems unnecessary and wholly ineffective.

COVID-19 Status

- **NCT04275414** is a 20 patient Phase II/III single-arm open-label study evaluating Avastin in adult patients (ages 18-80) who have confirmed COVID-19 infection and have respiratory distress. The **study's primary endpoint** is improvement in partial arterial oxygen pressure to fraction of inspiration O2. ***This study is expected to read out in the April/May timeframe***.
- **NCT04305106** is a larger 118 patient double-blind study in adults (ages 18-80) who have confirmed COVID-19 infection and have respiratory distress. The study has two arms, either IV Avastin or "no intervention." The study's primary endpoint is proportion of patients whose oxygenation index increased by 100mmhg on the 7th day after admission. ***This study is expected to read out in the June/July timeframe.***

Source: Company reports, Guggenheim Securities LLC Research

Antibody Approach – VIR / BIIB

Background and Mechanism

VIR Biotechnology is partnering with Biogen to develop and commercialize human monoclonal antibodies for the treatment of COVID-19. VIR said it has isolated several monoclonal antibodies from individuals who have survived SARS infection, that have been shown to bind to SARS-CoV-2 (Viral agent of COVID-19).

On March 25th the company announced that it is proceeding with two candidates to clinical studies. The antibody candidates bind to an epitope on SARS-CoV-2 that is shared with SARS-CoV-1. In addition, VIR has highlighted two modifications to the Fc region: 1) a half-life modification, potentially increasing coverage duration, and 2) a vaccinal mutation, intended to improve short-term potency and potentially provide long-term immunity (for a potentially prophylactic and therapeutic effect). The two candidates include one with and one without the vaccinal mutation.

The company also noted it has additional antibody candidates that bind to different binding sites (potentially to be used in combination) and intends to continue searching for antibody candidates.

Current Status / Commentary

This program is currently in preclinical development. The company expects Phase 1/2 testing to begin in ~3-5 months in summer 2020.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

APN 01 – GSK/Apeiron Biologics

Background and Mechanism

APN 01, a recombinant human angiotensin converting enzyme 2, (rhACE2) is being developed by Apeiron Biologics for the treatment of acute respiratory distress syndrome (ARDS) and less severe manifestations of acute lung injury (ALI) and pulmonary arterial hypertension (PAH).

The Renin Angiotensin System (RAS) affects the function of most organs, controlling important functions such as blood pressure and electrolytes. Target indications of the rhACE2 enhancement therapy are diseases that have an imbalance of the RAS system and insufficient natural ACE2 activity.

GSK did not pursue development of GSK 2586881 and thus Apeiron had obtained APN 01 licenses back from the firm. Development appears to have largely been discontinued.

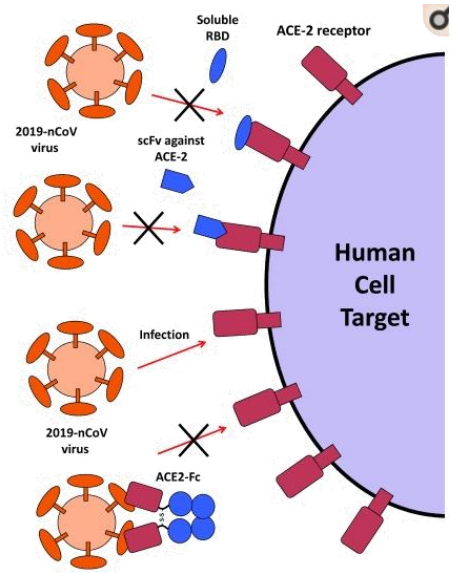
Product Characteristics

- **Not approved in the US** (Clinical development for ALI and PAH are underway in Canada, Germany, Spain and the US).

COVID-19 Status

APN01 is a recombinant human Angiotensin Converting Enzyme 2 (rhACE2) that was under Phase 2 clinical development in ALI and PAH. However, recently ACE2 has been shown to be the cellular entry receptor for the novel coronavirus SARS-CoV-2. Therefore, Apeiron is currently planning a clinical pilot study in China in patients infected with SARS-CoV-2 and is evaluating options for further clinical development.

The large spike protein on the surface of the coronavirus binds to ACE2 on infected cells, leading to cell entry. Target cells expressing ACE2 include lung tissues. Blocking the cell entry and avoiding infection could potentially be done through (1) a receptor-binding domain (RBD) of the spike protein from SARS or 2019-nCoV that binds ACE2 and saturates available sites, (2) an antibody or single chain antibody fragment (scFv), or (3) target the coronavirus virions directly by using the ACE2 extracellular domain as bait to bind to spike protein.



Sources: UpToDate; AdisInsight; Clin Sci (Lond). 2020 Mar 13;134(5):543-545.; F1000Res. 2020 Jan 31;9:72.

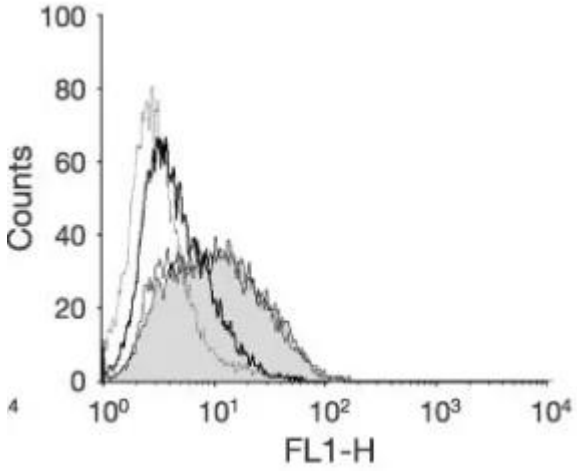
APN 01 – Relevant Preclinical / Clinical Data Summary

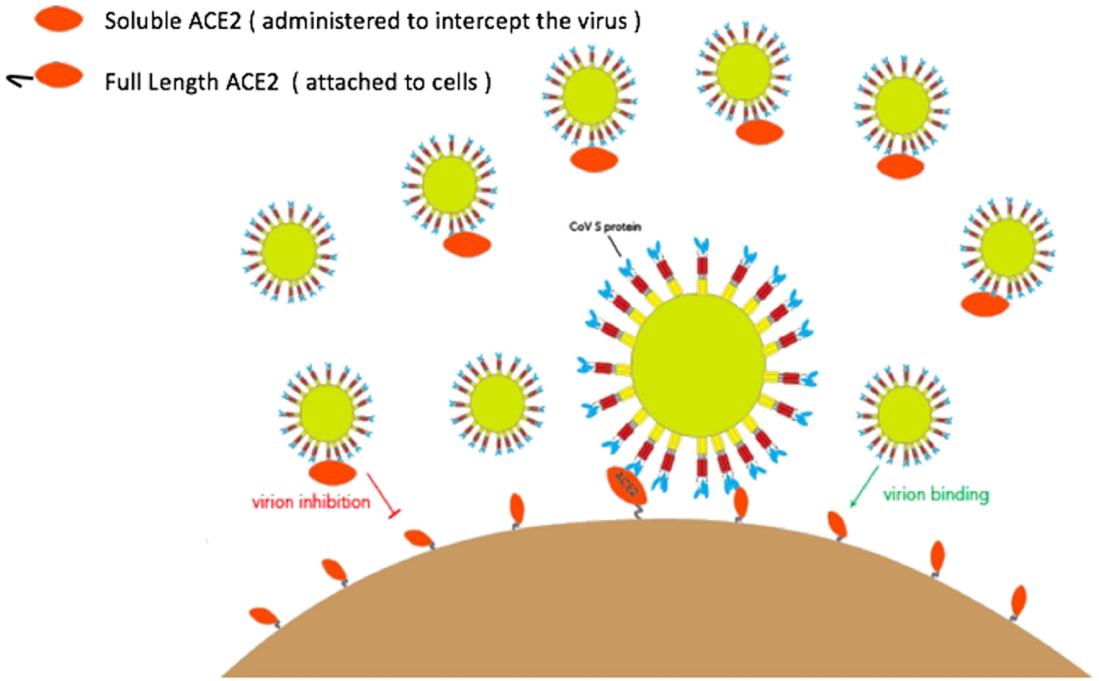
Soluble recombinant ACE2 may act as a competitive interceptor of SARS-CoV and other coronaviruses by preventing binding of the viral particle to the surface-bound, full-length ACE2. In vitro studies showed that SARS-CoV replication was blocked by a soluble form of ACE2 in the monkey kidney cell line, Vero-E6 (see below). Mouse models with only the human version of ACE2 could help expedite preclinical assessment of APN01.

The soluble form of ACE2 (isolated from SARS coronavirus (SARS-CoV)-permissive Vero E6 cells), but not of the related enzyme ACE1, blocked association of the S1 domain with Vero E6 cells and anti-ACE2 (but not anti-ACE1 antibody) blocked viral replication on Vero E6 cells, which indicates that ACE2 is a functional receptor for SARS-CoV.

Preclinical Trial Data

A soluble form of ACE2 (solid dark line), but not that of the related enzyme ACE1, blocked the association of S1–Ig with Vero E6 cells





Sources: UpToDate; AdisInsight; Clin Sci (Lond). 2020 Mar 13;134(5):543-545.; F1000Res. 2020 Jan 31;9:72.; Li W, et al. Nature 426, 450–454.

APN 01 – Ongoing Clinical Trials (Global)

Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2) was being evaluated in 1 trial, but most recently was recorded as a withdrawn trial due to it lacking CDE (Center for Drug Evaluation) approval.

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04287686 GIRH-APN01	A Randomized, Open Label, Controlled Clinical Study to Evaluate the Recombinant Human Angiotensin-converting Enzyme 2 (rhACE2) in Adult Patients With COVID-19	0 Withdrawn	The First Affiliated Hospital of Guangzhou Medical University	China	04/2020

Source: Clinicaltrials.gov; ChiCTR

STI-4398 (COVIDTRAP) – SRNE

Background and Mechanism

STI-4398 is a proprietary ACE2 (angiotensin-converting enzyme 2)-Fc fusion protein (COVIDTRAP). The STI-4398 protein binds to the S1 domain of the spike protein, which is expected to block the spike protein of the SARS-CoV-2 virus to bind the ACE2 receptors present on the target respiratory epithelial cells. Without the ability to penetrate target cells, the SARS-CoV-2 virus cannot replicate and spread itself.

The STI-4398 COVIDTRAP preserves the ACE2 enzyme activity in converting angiotensin II to angiotensin 1-7, resulting in reduced vasoconstriction and increased blood flow to the infected lung tissue. STI-4398 has been engineered to have a prolonged half-life in the human blood circulation.

Current Status / Commentary

Currently, STI-4398 is not approved anywhere for any use.

Product Characteristics

- **I.V. infusion**
- **ACE2 (angiotensin-converting enzyme 2)-Fc fusion protein**

COVID-19 Status

SRNE announced it has produced a preclinical batch of the STI-4398 (COVIDTRAP) protein to immediately commence testing its neutralization and blocking activity in preventing SARS-CoV-2 virus from infecting ACE2-expressing cells. In vitro cell studies for SARS-CoVID-2 virus infection and neutralization are expected to be conducted in the next few weeks in collaboration with world-leading coronavirus experts.

Sorrento scientists are in parallel working speedily to generate a stable CHO (Chinese Hamster Ovary) manufacturing cell line that would enable high-yield cGMP production of the COVIDTRAP fusion protein.

Sorrento currently anticipates it will complete the enabling studies for an expedited IND filing in the next few months.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Immunomodulatory Approaches for the treatment of COVID-19

1. Steroids / Thalidomide
2. IL-6 antibodies
3. Other

See pages 130 - 131 for analyst certification and important disclosures.

Corticosteroids

Background and Mechanism

Corticosteroids are a class of drug that suppress inflammation in the body, broadly encompassing both laboratory-synthesized and naturally produced hormones.

Corticosteroids are used for reducing symptoms like swelling, itching, redness, and allergic reactions; and commonly administered to patients with rheumatoid arthritis, chronic obstructive pulmonary disease, systemic lupus erythematosus, inflammatory bowel disease, and asthma. The drugs bring about their physiologic effects through numerous biochemical pathways, including inhibitory action on phospholipase A2, an enzyme critical to the production of inflammatory compounds, as well as other effects on gene expression, translation, and enzyme activity.

Product Characteristics

Oral, intranasal, topical, or intramuscular injection

Advantages include**:**

- Cheap and relatively easy to manufacture
- Rapid reduction in inflammation, well understood and widely used therapy

Limitations include:

- Numerous short-term adverse effects including mood swings, memory and behavior and other psychological effects, such as confusion or delirium, and weight gain
- Long-term side effects include osteoporosis, elevated pressure in the eyes (glaucoma), fluid retention, hypertension

Current Status

There are numerous approved branded and generic formulations of glucocorticoids that are approved and widely available with similar molecular structure and clinical effects, including cortisone, prednisone, prednisolone, methylprednisolone, and others.

Their major distinctions include potency (dose), duration, and mineralocorticoid (salt-retaining) activity, with selection of specific drugs determined by desired route of administration or duration of effect.

If proven safe and efficacious for treatment of COVID-19-related illness, corticosteroids could be administered to patients broadly and rapidly.

COVID-19 Status

Current interim guidance from WHO on clinical management of severe acute respiratory infection when novel coronavirus infection is suspected (released Jan 28, 2020) advises against the use of corticosteroids unless indicated for another reason.

A February 7, 2020 commentary published in The Lancet noted that corticosteroids suppress lung inflammation but also inhibit immune responses and pathogen clearance. Use of corticosteroids has been associated with adverse outcomes in SARS-CoV infection, including persistent inflammation after viral clearance and diffuse alveolar damage.

Currently, corticosteroid therapy is being evaluated in 3 clinical trials in China for COVID-19-realated pneumonia.

Source: Guggenheim Securities LLC Research

Corticosteroids Relevant Clinical Data Summary

Published data on corticosteroids for treatment of COVID-19 are not yet available, but a commentary published in The Lancet (Feb. 7, 2020) advises against using corticosteroid treatment for COVID-19 lung injury, citing outcomes from other respiratory viral infections (e.g. MERS-CoV, SARS-CoV).

- **MERS-CoV:** In a retrospective observational study reporting on 151 adults who were critically ill with MERS and given corticosteroids (median hydrocortisone equivalent dose 300 mg/day), patients who were given corticosteroids were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy.
- **SARS-CoV:** Four conclusive studies indicated harm, including a randomized controlled trial of 16 patients with SARS who were not critically ill in which the nine patients who were given hydrocortisone (mean 4·8 days [95% CI 4·1–5·5] since fever onset) had greater viremia in the second and third weeks after infection than those who were given 0·9% saline control.
- **Influenza:** A 2019 systematic review and meta-analysis identified ten observational studies in influenza, with a total of 6,548 patients. The investigators found increased mortality in patients who were given corticosteroids (risk ratio [RR] 1·75, 95% CI 1·3–2·4; p=0·0002). Among other outcomes, length of stay in an intensive care unit was increased (mean difference 2·1, 95% CI 1·2–3·1; p<0·0001), as was the rate of secondary bacterial or fungal infection (RR 2·0, 95% CI 1·0–3·8; p=0·04).

Virus	Outcomes of corticosteroid therapy	Comment
MERS-CoV	Delayed clearance of viral RNA from respiratory tract	Adjusted hazard ratio 0·4 (95% CI 0·2–0·7)
SARS-CoV	Delayed clearance of viral RNA from blood	Significant difference but effect size not quantified
SARS-CoV	Complication: psychosis	Associated with higher cumulative dose, 10 975 mg vs 6780 mg hydrocortisone equivalent
SARS-CoV	Complication: diabetes	33 (35%) of 95 patients treated with corticosteroid developed corticosteroid-induced diabetes
SARS-CoV	Complication: avascular necrosis in survivors	Among surviving patients (n=40), 12 (30%) avascular necrosis and 30 (75%) osteoporosis
Influenza	Increased mortality	Risk ratio for mortality 1·75 (95% CI 1·3–2·4) in a meta-analysis of 6548 patients from ten studies
RSV	No clinical benefit in children	No effect in largest randomized trial of 600 children, of whom 305 (51%) were treated with corticosteroids

Source: Russell et al The Lancet 2020, Guggenheim Securities LLC Research

Corticosteroids Ongoing Clinical Trials (Global)

Corticosteroids are currently being evaluated in 3 trials globally for treatment of COVID-19

NCT ID / trial link	Title	Enrollment	Sponsor	Geography	Primary Est. Completion
NCT04273321	Efficacy and Safety of Corticosteroids in COVID-19	N=400	Beijing Chao Yang Hospital	China	05/01/2020
ChiCTR2000030481	The clinical value of corticosteroid therapy timing in the treatment of novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial	N=200	Zhongnan Hospital of Wuhan University	China	4/30/2020
NCT04244591	Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure (Steroids-SARI)	N=80	Peking Union Medical College Hospital	China	04/25/2020

Source: clinicaltrials.gov, Guggenheim Securities LLC Research

Thalidomide

Background and Mechanism

Thalidomide (BMY) is an oral immunomodulatory drug capable of modulating and regulating immune response.

Thalidomide was originally marketed as an over-the-counter sedative in the 1950s & 1960s. In the early 1960s, Australian obstetrician Dr. William McBride reported that Thalidomide also had an anti-nausea effect in his pregnant subjects, which led to a large off-label use of Thalidomide in this setting. Soon after this wide uptake, it was discovered that Thalidomide has teratogenic properties that were disrupting normal embryo development in pregnant patients and resulting in the infamous catastrophic birth defects. This tragedy eventually led to substantial changes to FDA processes and drug approval requirements. As a result, Thalidomide was not approved in the U.S. until 1998 when it was reborn as an anti-cancer agent for the treatment of multiple myeloma, a disease primarily among patients not in prime reproductive years. Studies have elucidated that Thalidomide's mechanism of action includes (a) inhibition of IL-6, a growth factor in cell proliferation, and (b) activation of apoptotic pathways through caspase 8-mediated cell death.

Product Characteristics

- **Oral Tablet**
- **Uses an FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) program**
- **Contraindicated in pregnant women**

Current Status

Thalidomide is currently approved for use in the treatment of multiple myeloma and moderate-to-severe erythema nodosum leprosum.

COVID-19 Status

Thalidomide, an immunomodulator and anti-inflammatory agent, has been shown to stimulate T-cells, inhibit cell proliferation, and reduce lung injury and pulmonary fibrosis. As such, it is being evaluated as a treatment option for COVID-19.

A non-peer reviewed case study from Wencheng County People's Hospital was posted in late February. The case details a 45-year old woman with presenting symptoms of cough, fever, fatigue, and diarrhea. The patient was initially treated with ofloxacin and oseltamivir, but the infection persisted and on Feb. 5, 2020 (hospital day 2) the patient began treatment with Thalidomide in combination with low dose methylprednisolone. The patient's condition improved with increased oxygen index, resolved nausea and vomiting, and decreased cytokine levels back within normal range.

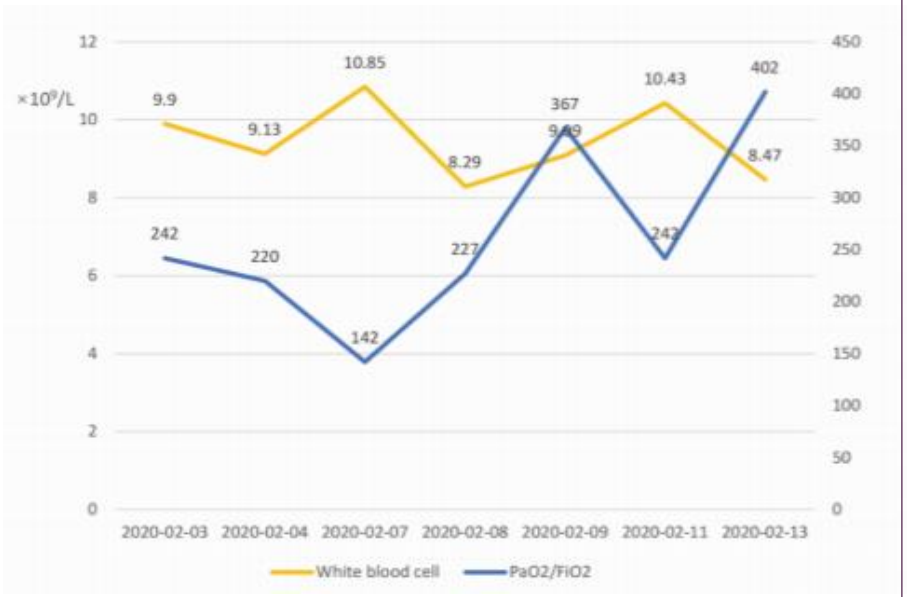
Source: Guggenheim Securities LLC Research

Thalidomide – Relevant Clinical Data Summary

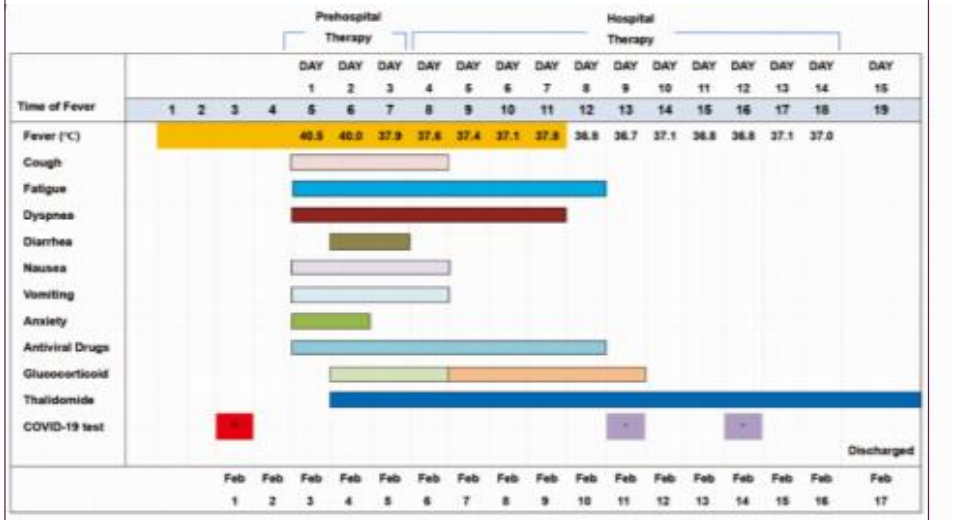
A non-peer reviewed case study of a 45-year old woman was reported. The patient was initially stable at the time of admission but was experiencing deterioration by Day 2 in the hospital (e.g. high fever, dyspnea, fatigue, nausea, vomiting, decreased oxygenation index), which led to the classification of the patient into the "severe" patient grouping. On Day 2, the patient was treated with 100mg Thalidomide every 24 hours and low-dose methylprednisolone.

The patient's condition improved in a matter of days post-treatment (Feb. 5). The patient's oxygen index increased, and nausea and vomiting were resolved within 1-3 days. By Feb. 10, the absolute lymphocyte increased from 0.39 × 109 /L to 1.39 × 109 /L, T cells from 254 to 788/μL, CD4 + T cells from 163 to 438/μL, CD8+T. By Feb. 11, cytokine levels returned to the normal range including IL-6 at 1.24 pg/mL, IL-10 at 3.28 pg/mL and IFN-γ at 0.10 pg/mL.

Dynamic course of the total number of white blood cells and the oxygen index during hospitalization.



Symptoms, body temperatures and drug use according to the day of illness and day of hospitalization, Feb. 3 to Feb. 17



Source: Guggenheim Securities LLC Research; https://www.preprints.org/manuscript/202002.0395/v1

Thalidomide – Ongoing Clinical Trials (Global)

Thalidomide is currently being evaluated in 2 trials globally.

NCT ID / trial link	Title	Enrollment	Sponsor	Geography	Primary Est. Completion
NCT04273529	The Efficacy and Safety of Thalidomide in the Adjuvant Treatment of Moderate New Coronavirus (COVID-19) Pneumonia	N=100	First Affiliated Hospital of Wenzhou Medical University	China	5/30/20
NCT04273581	The Efficacy and Safety of Thalidomide Combined With Low-dose Hormones in the Treatment of Severe COVID-19	N=40	First Affiliated Hospital of Wenzhou Medical University	China	4/30/20

Source: Guggenheim Securities LLC Research; clinicaltrials.org

IL-6R Overview

IL-6 is a pleiotropic cytokine that is often pro-inflammatory and signals through a receptor complex composed of both GP80 and GP130 subunits (GP130 is the signal transduction unit that leads to Stat-3 phosphorylation). The cytokine is involved in mediating fever, the acute phase response, and can stimulate production of neutrophils and B-cells. IL-6 is overexpressed during a variety of inflammatory diseases.

Mechanism behind IL-6R inhibition

- By targeting IL-6 or the IL-6 receptor, transduction of the IL-6 signal can be halted. In cases of severe inflammation, this helps to reduce or stop the fever, acute phase response, and/or other (potentially deadly) inflammatory events patients are suffering from, while also ending the dangerous feed-forward loop that can develop in these cases.

IL-6/ IL-6R antibodies under development for COVID-19

- Two IL-6R antibodies are currently under development for the treatment of severe COVID-19; REGN's Kevzara (sarilumab), and RHHBY's Actemra (toclizumab). Both antibodies can bind both membrane-bound and soluble IL-6R, shutting down IL-6 signaling. Kevzara is approved to treat adult patients with moderate to severe active rheumatoid arthritis, while Actemra is approved to treat adults with moderately to severely active rheumatoid arthritis (RA), adults with giant cell arteritis (GCA), and children ages two and above with Polyarticular Juvenile Idiopathic Arthritis (PJIA) or Systemic Juvenile Idiopathic Arthritis (SJIA).
- EUSA's SYLVANT (siltuximab) is a chimeric monoclonal antibody to IL-6. It's currently approved for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.

IL-6/ IL-6R antibody status in COVID-19

- There is currently one ongoing Kevzara trial and five Actemra trials evaluating these drugs in COVID-19. Actemra has already completed one small exploratory study in 20 patients in China in late 2019, generating positive data, indicating enhanced survival and reduced lethality from severe infection. Initial results (non-peer reviewed) from the Actemra trial found that treatment with Actemra resulted in COVID-19 patients experiencing rapidly reduced fevers, 75% of patients (15 out of 20) reduced their need for supplemental oxygen within days of receiving Actemra, and 52.6% (10/19) patients had lymphocytes in peripheral blood return to normal levels on the fifth day after treatment. Based on these results, China recently updated its COVID-19 treatment guidelines and approved the use of that IL-6 inhibitor to treat patients with severe or critical disease. ***In our view, this trial, having already generated positive data has helped to de-risk this mechanistic approach towards treating severe COVID-19 cases.***
- SYLVANT is currently being evaluated in a trial (SISCO Study) sponsored the Papa Giovanni XXIII Hospital in Italy. The study will investigate two cohorts retrospectively, hospitalized patients prior to admission to an intensive care unit (ICU) or patients already requiring intensive care, and will compare to matched controls. Primary endpoints are reduction in the need for invasive ventilation, time spent in ICU or 30-day mortality. Initial data are expected in late March 2020.

Source: Guggenheim Securities LLC Research

IL-6R Antibody COVID-19 Trials

Kevzara (REGN)

NCT04315298 is a Phase II/III double-blind placebo-controlled study (n=400) started on March 16, 2020 and is expected to complete within 1 year. The trial will use two doses (high and low) of Kevzara alongside placebo. The **primary endpoint** is time-to-resolution of fever for at least 48h without antipyretics for 48h (up to day 29). The trial will enroll adults (age 18+) who have lab confirmed SARS-CoV-2 and hospitalized with illness with evidence of pneumonia or multi-system organ dysfunction. As of 3/21/20, 10 patients were enrolled in this trial.

SYLVANT (EUSA Pharma/BGNE)

SISCO Study is an observational case-control trial of siltuximab, sponsored by the Papa Giovanni XXIII Hospital in Italy, for the treatment of patients infected with COVID-19 who develop serious respiratory complications. The study represents the data collection and analysis of a series of patients treated under an ongoing emergency compassionate use protocol. The study will investigate two cohorts retrospectively: hospitalized patients prior to admission to an intensive care unit (ICU) or patients already requiring intensive care, and will compare to matched controls. Primary endpoints are reduction in the need for invasive ventilation, time spent in ICU or 30-day mortality. Initial data are expected in late March 2020.

Actemra (RHHBY)

ChiCTR2000029765 (n=188) is a prospective placebo-controlled study to evaluate the efficacy and safety of tocilizumab in treating regular patients with NCP (including severe risk factors) and critical NCP patients (including those with COVID-19) who have elevated IL-6 levels.

NCT04310228 is an open-label (n=150) trial evaluating Actemra alone or in combo with favipiravir (a replicase inhibitor antiviral drug). A favipiravir-only group will serve as an active control. The study's **primary endpoint** is the clinical cure rate over 3 months. The study began March 8, 2020, and has an estimated completion date in May of 2020.

NCT04315480 is an open-label Phase II (n=30) study using Simon's two-stages optimal design. The study's **primary endpoints** are arrest in deterioration of pulmonary function, and improvement in pulmonary function (both over 7 days). The study began in March 2020 and is estimated to wrap up in the April/May 2020 timeframe.

NCT04317092 is an open-label Phase II (n=330) study using 8 mg/kg Actemra (up to 800mg per dose) with a 12h interval. **The primary endpoint** is the one-month mortality rate (up to 1 month). The study began in March 2020 and is expected to run through December 2020.

COVACTA is a double-blind, placebo-controlled Phase III trial that is currently being planned by Roche, to be conducted in concert with BARDA. The study will focus on adult patients hospitalized with severe COVID-19 pneumonia. **The primary and secondary endpoints** include clinical status, mortality, mechanical ventilation and intensive care unit (ICU) variables. Patients will be followed for 60 days post-randomization, and an interim analysis will be conducted to look for early evidence of efficacy.

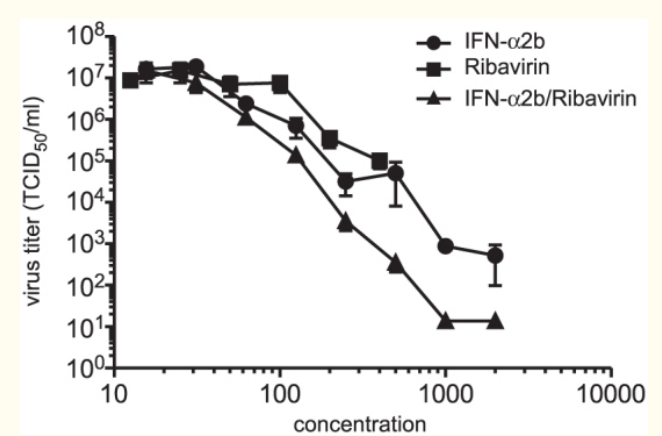
Source: Guggenheim Securities LLC Research and www.clinicaltrials.gov

Recombinant Human Interferon α-2b (IFN-α2b / rhIFN-α2b)

Background and Mechanism

IFN-α2b was trialed along with ribavirin for MERS-CoV and hCoV-EMC in Saudi Arabia and currently it is also being trialed in a similar combination in China for the COVID-19.

In an in vitro study for hCoV-EMC, the combination showed an additional reduction in the virus titer by 0.4- to 2.16-logs over that of IFN-α2b treatment alone.



Limited information on IFN-α2b product.

Product Characteristics

- **Subcutaneous injection or nebulization inhalation (as used in the trials)**
- **Not approved in the US**
- *Limited information on IFN-α2b*

COVID-19 Status

MERS CoV: Omrani et al[12] reported that treatment with ribavirin and pegylated IFN-α2a (180 µg subcutaneously once per week for 2 weeks) significantly improves survival 14 days after the diagnosis of MERS CoV infection (P=.004). Enhanced survival 28 days after diagnosis in patients who received ribavirin and pegylated IFN-α2a was not statistically significant (P=.054). In this case series of n=6 patients with MERS CoV infection, n=4 had symptomatic disease with pneumonia and respiratory failure, while n=2 were asymptomatic close contacts of infected patients who tested positive. N=3/6 who had comorbid conditions died during the study period, while n=3 had successful outcomes. The diagnosis and treatment was delayed by an average of 15 days in those patients who died.

COVID-19: New coronavirus infection is an important cause of public health emergencies at home and abroad, which seriously affects people's health and social stability. The outbreak of SRAR-COV in China in 2003 caused serious social impact. From January 2002 to August 7, 2003, there were a total of 8,422 cases worldwide, involving 32 countries and regions, of which 919 cases were fatal, with a fatality rate of nearly 11%. The fatality rate of elderly patients and patients with underlying diseases was even higher.

There is no precise and effective treatment for coronavirus infection. In vitro, IFN-α2β has inhibitory effects on MERS-CoV and closely related coronavirus severe acute respiratory syndrome (SARS) -CoV. A study showed the effects of interferon-α2β and ribavirin on the replication of nCoV isolates hCoV-EMC / 2012 in Vero and LLC-MK2 cells. The combined application may be useful for the management of patients with nCoV infection in the future. At present, the combination therapy of interferon α2β and ribavirin has been successfully applied in the initial treatment and prevention of SARS and MERS.

The purpose of the NCT04293887 study in China at the Tongji Hospital is to evaluate the efficacy and safety of recombinant human interferon α1β in treating patients with new coronavirus infection in Wuhan.

Sources: UpToDate; AdisInsight; ClinicalTrials.gov; NCT04293887; Sci Rep. 2013; 3: 1686.; Ann Saudi Med. 2014 Sep-Oct;34(5):396-400.

IFN-α2b / rhIFN-α2b – Ongoing Clinical Trials (Global)

Interferon, or specifically, recombinant human interferon α-2b (IFN-α2b / rhIFN-α2b), is currently being evaluated in 4 trials and is additionally included as a potential treatment in control arms of 8 other studies (NCT04251871 [TCM], NCT04275388 [Xiyanping Injection], NCT04273763 [Bromhexine HCl], NCT04314817 [Safety trial], NCT04291729 [Ganovo/Danoprevir], NCT04295551 [Xiyanping Injection], NCT04273581 [Thalidomide], NCT04269525 [Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs)]).

In China, there are an additional 13 trials being conducted where interferon may be part of the control arm or being assessed primarily: ChiCTR2000029387, ChiCTR2000029600 (Favipiravir), ChiCTR2000029638, ChiCTR2000029756 (Xiyanping Injection), ChiCTR2000029989 (eye drops), ChiCTR2000030013 (spray), ChiCTR2000030082 (dihydroartemisinine piperaquine), ChiCTR2000030117 (Xiyanping Injection), ChiCTR2000030166 (Qing-Wen Bai-Du-Yin), ChiCTR2000030480, ChiCTR2000030535 (Ebastine), ChiCTR2000030854, and ChiCTR2000030922 (+ ribavirin).

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04254874	A Prospective/Retrospective, Randomized Controlled Clinical Study of Interferon Atomization in the 2019-nCoV Pneumonia	100	Tongji Hospital	China	06/2020
NCT04293887	Efficacy and Safety of IFN-α2b in the Treatment of Novel Coronavirus Patients	328	Tongji Hospital	China	05/2020
NCT04276688	Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	70	The University of Hong Kong	Hong Kong	01/2022
NCT04315948	Trial of Treatments for COVID-19 in Hospitalized Adults	3200	Institut National de la Santé et de la Recherche Médicale (INSERM)	France	03/2023

Source: Clinicaltrials.gov; ChiCTR

Esbriet (Pirfenidone / Pirespa / Etuary) – ROG-SWX

Background and Mechanism

Pirfenidone is an orally active synthetic, anti-fibrotic, anti-inflammatory, small-molecule drug developed by ROG-SWX for the treatment of acute lung injury, diabetic nephropathies, renal failure, heart failure, interstitial lung disease, interstitial pulmonary fibrosis (IPF), for the prevention of lung transplant rejection and graft versus host disease (GVHD).

Pirfenidone acts with a multi-modal mechanism as it suppresses excessive collagen deposition, down-regulates production of multiple cytokines, and slows the tumor cell proliferation and stimulation in response to cytokines. It also inhibits DNA synthesis and the production of mRNA for collagen types I and III, resulting in a reduction in radiation-induced fibrosis.

It was first launched in Japan for IPF in December 2008 by Shionogi.

Product Characteristics

- **Oral Tablet and Capsule**
- **Approved in the US (2014) for IPF**
- **Has multiple potential adverse events as follows.** Common adverse effects with at least 10% incidence include: nausea, rash, abdominal pain, upper respiratory tract infection, diarrhea, fatigue, headache, dyspepsia, dizziness, vomiting, anorexia, gastro-esophageal reflux disease, sinusitis, insomnia, weight decreased, and arthralgia. Should be taken with food.
- **Recommended maintenance dose is 801 mg three times daily (2403 mg/day).**

COVID-19 Status

The drug is being studied in patients with severe and critical COVID-19 through a randomized, open-label clinical trial that has been prospectively registered by Tongji Hospital of Tongji Medical College, part of Huazhong Science and Technology University.

This trial has a primary completion date of April 2020, so accordingly, we look forward to seeing initial data within the following month.

The drug is also being trialed within the First Affiliated Hospital of Guangzhou Medical University.

Sources: UpToDate; AdisInsight; Package Insert; JNJ Press Release

Esbriet – Ongoing Clinical Trials (Global)

Esbriet (Pirfenidone / Pirespa / Etuary) is currently being evaluated in 2 trials in China.

The first study had planned to randomize ~147 adult subjects in the active group and the study design included stratification based on whether the onset time is ≤ 14 days. Subjects would be randomly divided into two treatment groups (1:1), with the active group receiving standard treatment or pirfenidone orally TID (3 times a day), 2 tablets each time for a total course of 4 weeks or more. Subjects and all research center staff were not blinded.

Patients would be assessed at Week 4 with a chest CT, finger pulse oxygen, blood gas change from baseline, and K-BILD (absolute change in total score of King's brief questionnaire for interstitial pulmonary disease).

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
NCT04282902 ChiCTR2000030333	A Randomized, Open-label Study to Evaluate the Efficacy and Safety of Pirfenidone in Patients With Severe and Critical Novel Coronavirus Infection	294	Huilan Zhang / Tongji Hospital	China	04/2020
ChiCTR2000030892	Efficacy and Safety of Pirfenidone in the Treatment of Severe Post-Novel Coronavirus Pneumonia (COVID-19) Fibrosis: a prospective exploratory experimental medical study	40	The First Affiliated Hospital of Guangzhou Medical University	China	- Started on 03/2020

Source: Clinicaltrials.gov; ChiCTR

Ebastine – Almirall / SAN-PAR

Background and Mechanism

Ebastine is a piperidine derivative and is a prodrug of carebastine, a histamine H1 receptor antagonist. It also has histamine H1-receptor antagonist properties, but lacks sedative and antimuscarinic activity.

It originated from the Spanish company Almirall Prodesfarma (now Laboratorios Almirall; BME: ALM), and is approved for the treatment of allergic rhinitis and chronic idiopathic urticaria in more than 30 countries worldwide.

Ebastine is licensed to Sanofi (SAN-PAR) for marketing and development in France, Belgium, the Netherlands, Germany, the UK, North and South America, Russia and Scandinavia.

Product Characteristics

- **Oral Tablet**
- **Not approved in the US (but has launched in 20+ countries for seasonal and perennial allergic rhinitis and idiopathic chronic urticaria)**
- **Relatively well tolerated.** Common adverse effects include: headache, dry mouth and drowsiness. Can be taken without regard to food.
- **The recommended dosage is one tablet (10mg) once a day.**
- **Given that the product is genericized, the medication would be cheap to manufacture.**

COVID-19 Status

There are no published studies with ebastine in any coronavirus (including SARS or MERS)-related disease, including in vitro studies for COVID-19.

However, it is being trialed in China in combination with interferon-alpha aerosol inhalation BID and Lopinavir (vs. the interferon-alpha aerosol inhalation BID and Lopinavir combination alone). ChiCTR does not report estimated primary completion dates, but the trial did start in March 2020 so we expect results in 2H 2020, at the minimum.

Notably, the trial assesses ebastine in a BID dosing regimen vs. its approved QD schedule.

Sources: UpToDate; AdisInsight; Package Insert/Leaflet

Ebastine – Ongoing Clinical Trials (Global)

Ebastine is currently being evaluated in 1 trial in China as part of a randomized clinical trial with parallel assignment to treatment arms: (1) ebastine 10mg BID, interferon-alpha aerosol inhalation 5 million units BID and Lopinavir 200 mg (2 capsules at a time) BID and (2) the control group: interferon-alpha aerosol inhalation 5 million units BID and Lopinavir 200 mg (2 capsules at a time) BID.

The trial is assessing the clinical therapeutic course, defined as fever, respiratory rate, blood oxygen saturation turned to normal and cough relieved for at least 72 hours along with chest CT showing inflammation was obviously absorbed, and with the nucleic acid of respiratory pathogens being detected as negative twice in a row (the sampling interval was at least 1 day).

NCT ID / Trial Link	Clinical Trial Title	Enrollment (N)	Sponsor	Geography	Primary Est. Completion
ChiCTR2000030535	Multi-Center Clinical Study on the Treatment of Patients with Novel Coronavirus Pneumonia (COVID-19) by Ebastine	100	Mianyang Central Hospital	China	- *Started on 03/2020*

Source: Clinicaltrials.gov; ChiCTR

PD-1 antibody – Southeast University, China

Background and Mechanism

PD-1 is an immunosuppressive receptor preferentially expressed on T-cells, which helps to regulate the balance between cell activation, senescence, and apoptosis. Given that hyperactive T-cells play a role in the perpetuation of sepsis in septic patients, and the similarities in the heavy inflammation shared between sepsis and the severe pneumonia in some COVID-19 patients, Southeast University in China is beginning a trial to evaluate a PD-1 antibody in patients with severe pneumonia associated with lymphocytopenia in COVID-19 infection. The hope is that by using a PD-1 antibody to reduce T-cell activation in these patients, some of the extreme lung inflammation can be prevented/reduced, effectively promoting more rapid recovery and survival in pneumatic patients.

Current Status / Commentary

This approach would not actually help to reduce or clear infection, it would only be intended to combat some level of severe/fatal inflammation that occurs in the worst cases of pneumonia. It's unclear what the T-cell contribution is to the pneumonia seen in COVID-19 patients, or if the pneumonias carry particular commonalities. Without this information, it's challenging to make even a cursory judgement as to the probability of success here. However, given the existing positive preliminary data for the IL-6R antibodies, we would be inclined to view those as a more de-risked approach in COVID-19 vs. the PD-1 approach.

Product Characteristics

Multiple PD-1 antibodies are approved across a wide array of cancers, though the particular one being evaluated here is not presently clear.

COVID-19 Status

This trial (n=120; NCT04268537) is a single-blind, placebo-controlled three arm trial. **Arm 1** is Anti-PD-1 antibody, 200mg, IV, one time, **Arm 2** is Thymosin, 1.6 mg sc qd, last for 5 days, and **Arm 3** is placebo. This study's **primary endpoint** is proportion of lung injury score decreased 1 or more points, with key secondary endpoints including lymphocyte counts, inflammatory cytokine levels, and SOFA score. Per clinicaltrials.gov, the study's estimated primary completion date is April 30, 2020.

Source: Guggenheim Securities LLC Research

Other Modalities for the treatment of COVID-19

1. Mesenchymal stem cells
2. Other

Mesenchymal Stem Cells

Background and Mechanism

Mesenchymal stem cells (MSCs) are multipotent, self-renewable non-hematopoietic stem cells that are able to differentiate into multiple tissues including bone, cartilage, muscle and fat cells, and connective tissue. MSCs also have immunomodulatory features including cytokine & immune receptor secretion that can regulate the host's tissue microenvironment.

MSCs were first isolated and characterized by Friedenstein & colleagues in 1974. It has since been elucidated that MSCs exist in almost all tissues and are easily isolated from the bone marrow, adipose tissue, etc. Given their role in growth, wound healing, and replacing cells, MSCs have shown benefit when used for injury repair including patients with liver failure, corneal damage, and brain/spinal cord injuries. Additionally, given their role in regulating immune responses, MSCs have shown benefit in GVHD, lupus, Crohn's disease, and multiple sclerosis. Further investigations have confirmed that MSCs tend to home in on damaged tissue sites.

Product Characteristics

- **Can be autologous or allogeneic.**
- **Has been evaluated in thousands of patients with various underlying disease states (e.g. neurodegenerative, CV, IBD, etc.).**
- **Heterogeneity of MSC origin and harvesting protocol has limited consistency of data conclusions;** No well-established/ standardized protocol for MSC isolation and ex vivo preparation.

Current Status

Mesenchymal stem cell transplant is not FDA-approved despite numerous positive clinical trial findings; however, MSC transplant is approved for use in Europe, Canada, and Australia.

COVID-19 Status

Several reports have suggested that the first step of HCoV-19 pathogenesis involves recognition of ACE2 receptors on host cells, similar to infection by SARS-2003. While ACE2 receptors are widely expressed on various healthy human cells (e.g. alveolar type II cells and capillary endothelium), immune cells (e.g. B cells, T cells, and macrophages) are typically ACE2. That said, these cells may not have adequate immunomodulatory capacity to combat the virus' ability to stimulate a cytokine storm within the host's lungs. MSCs on the other hand, with well-demonstrated immunomodulatory effects, may be able to prevent or moderate a viral-induced cytokine storm.

A study evaluating MSCs in 10 patients with confirmed HCoV-19 pneumonia was conducted at Beijing YouAn Hospital in China in which 7 patients received MSC therapy and 3 received placebo. Patients were then followed for 14 days. In all 7 patients transplanted with MSCs, pre-transplant symptoms including fever, weakness, shortness of breath, and oxygen saturation were resolved within 2-4 days of MSC transplantation and oxygen saturation increased to ≥95% at rest. Furthermore, in a critically severe patient, inflammation was quickly and drastically reduced (plasma C-reaction protein decreasing from 105.5g/dL to 10.1g/dL over the 14 days). Also, there was evidence of regained pulmonary alveoli function with oxygen saturation without supplementary oxygen increased from 89% to 98%.

Source: Guggenheim Securities LLC Research; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4002895/ ; http://www.aginganddisease.org/EN/10.14336/AD.2020.0228#1

Mesenchymal Stem Cells – Relevant Clinical Data Summary

10 patients were enrolled into the study of which 7 were treated with MSCs and 3 were given placebo control. Clinical grade MSCs were supplied by Shanghai University, Qingdao Co-orient Watson Biotechnology, and Institute of Basic Medical Sciences. Prior to infusion, the cells were suspended in 100mL saline and each dose was calculated by 1x10^6 cells/kg. Patients were then assessed over the 14-day study period.

Clinical Classification of COVID-19 Per the National Health Commission of China

Mild	Common	Severe	Critically severe
Mild clinical manifestation, None Imaging Performance	Fever, respiratory symptoms, pneumonia performance on X-ray or CT	Meet any of the followings: 1. Respiratory distress, RR ≥ 30/min; 2. Oxygen saturation ≤ 93% at rest state; 3. Arterial partial pressure of oxygen (PaO_2) / Fraction of inspiration O_2 (FiO_2) ≤ 300mnHg, 1mmHg=0.133kPa	Meet any of the followings: 1. Respiratory failure needs mechanical ventilation; 2. Shock; 3. Combined with other organ failure, patients need ICU monitoring and treatment

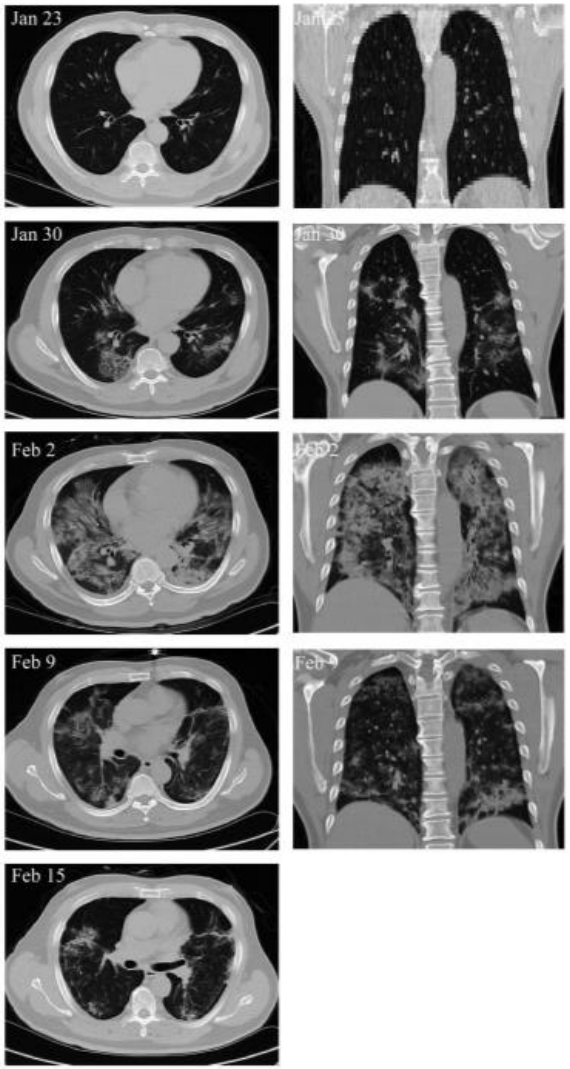
Enrolled Patient Baseline Characteristics

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Ctrl 1	Ctrl 2	Ctrl 3
Gender	M	F	F	F	M	M	M	F	F	F
Age (years)	65	63	65	51	57	45	53	75	74	46
COVID-19 type	Criticall y severe	Severe	Severe	Common	Common	Severe	Severe	Severe	Severe	Sever e
Fever (°C, baseline)	38.6	37.7	38.2	38.5	38.4	39.0	39.0	36.0	38.9	37.7
Shortness of breath	+++	+++	++	+	+	+++	+++	+++	++	+
Oxygen saturation at rest state	89%	93%	92%	95%	94%	92%	90%	91%	92%	93%
Cough, weak, poor appetite	++	+	++	+	++	++	++	+	++	+
Diarrhea	-	-	+	-	-	-	-	-	-	-
Date of diagnosed	Jan 23	Jan 27	Jan 25	Feb 3	Feb 2	Jan 27	Feb 3	Feb 3	Feb 6	Feb 5
Date of intervention (MSCs or Placebo)	Jan 31	Feb 2	Feb 4	Feb 4	Feb 4	Feb 6	Feb 6	Feb 8	Feb 6	Feb 6
Date of recovery	Feb 3	Feb 4	Feb 6 Discharged	Feb 6 Discharged	Feb 5 Discharged	Feb 7	Feb 7	Dead	ARDS	Stable

Source: Guggenheim Securities LLC Research; http://www.aginganddisease.org/EN/10.14336/AD.2020.0228#1

Mesenchymal Stem Cells – Relevant Clinical Data Summary

CT Images of Patient 1 (Critically Severe)



The study included a case study of a 65-year old man that had critically severe COVID-19 infection upon enrollment in the trial. *Following MSC transplantation on 1/31/2020, inflammation was quickly and drastically reduced per plasma C-reaction protein analysis and there was evidence of regained pulmonary alveoli function per oxygen saturation analysis. The CT scans (left) show the total invasion of the pneumonia on 2/2/2020 which began to subside in subsequent scans on 2/9/2020 and 2/15/2020. By Day 4 post-MSC transplantation, the patient's respiratory rate had decreased to the normal range, and the baseline fever and shortness of breath had resolved. Additionally, biochemical indicators of the patient's severe liver and myocardium damage as a result of the viral infection were back within the normal range 2-4 days post-treatment.*

Key Metrics Assessed from Patient 1 (Critically Severe)

	Home	Hospital	Hospital	ICU	ICU	ICU	ICU	ICU	Out of ICU	Hospital	Hospital
Date	Jan 21~22	Jan 23	Jan 24~29	Jan 30	Jan 31	Feb 1	Feb 2~3	Feb 4	Feb 5~8	Feb 9~12	Feb 13
Fever (℃)	37.5	37.8	37.0~38.5	38.6	38.8	36.8	36.6~36.9	36.8	36.6~36.8	36.5~36.9	36.6
Shortness of breath	–	+	+	++	++++	++	+	–	–	–	–
Cough	+	+	+	++	++	+	+	–	–	–	–
Sputum	+	+	+	++	++	+	+	–	–	–	–
O_2 saturation (without/with O_2 uptake)	NA/NA	NA/NA	97% /NA	91%/ 95%	89% /94%	NA /98%	NA /97%	NA /96%	NA /97%	96% //NA	97% /NA
Respiratory rate	NA	23	23	27	33	22	22	21	20~22	20~22	21
Treatment (Basics-1: Antipyretic, antiviral and supportive therapy. Basics-2: antiviral and supportive therapy)	NA	NA	Basics-1	Basics -1; Mask O_2 5L/min	Basics-1; Mask O_2 10L/min ; Cell transplant	Basics -1; Mask O_2 5L/min	Basics-2; Mask O_2 5L/min	Basics -2; Mask O_2 5L/min	Basics-2; Mask O_2 5L/min	Basics-2	Basics-2
RT-PCR of the virus	NA	Positive	NA	NA	NA	NA	NA	NA	Positive (Feb 6)	NA	Negative

Source: Guggenheim Securities LLC Research; http://www.aginganddisease.org/EN/10.14336/AD.2020.0228#1

Mesenchymal Stem Cells – Ongoing Clinical Trials (Global)

Mesenchymal stem cell-based therapy is currently being evaluated in 12 trials globally.

NCT ID / trial link	Title	Enrollment	Sponsor	Geography	Primary Est. Completion
NCT04313322	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	N=5	Stem Cells Arabia	Jordan	6/30/20
NCT04288102	Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019(COVID-19)	N=60	Beijing 302 Hospital	China	12/31/20
NCT04315987	Mesenchymal Stem Cell NestCellÂ® to Treat Patients With Severe COVID-19 Pneumonia	N=6	Azidus Brasil	Brazil	5/2020
NCT04252118	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	N=20	Beijing 302 Hospital	China	12/2020
NCT04302519	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	N=24	CAR-T (Shanghai) Biotechnology Co., Ltd.	China	6/30/21
NCT04273646	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia	N=48	Wuhan Union Hospital, China	China	6/30/20
NCT04269525	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(nCOV) Pneumonia	N=10	ZhiYong Peng	China	4/30/20
NCT04276987	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	N=30	Ruijin Hospital	China	5/31/20
ChiCTR2000030944	Clinical study of human NK cells and MSCs transplantation for severe novel coronavirus pneumonia (COVID-19)	N=20	The Second Affiliated Hospital of Nanchang University	China	8/31/20
ChiCTR2000030835	Clinical study for the efficacy of Mesenchymal stem cells (MSC) in the treatment of severe novel coronavirus pneumonia (COVID-19)	N=20	The First Affiliated Hospital of Xinxiang Medical University	China	2/14/20
ChiCTR2000030484	HUMSCs and Exosomes Treating Patients with Lung Injury following Novel Coronavirus Pneumonia (COVID-19)	N=90	Hubei Shiyan Taihe Hospital	China	1/31/20
ChiCTR2000030300	Umbilical cord mesenchymal stem cells (hucMSCs) in the treatment of high risk novel coronavirus pneumonia (COVID-19) patients	N=9	Nanjing Second Hospital	China	2/20/21

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Alpha-lipoic acid (ALA)

Background and Mechanism

Alpha-lipoic acid is an 8-carbon dithiol compound derived from octanoic acid with antioxidant activities and is organically produced in the human body.

α-Lipoic acid has been applied for the treatment of polyneuropathies and hepatic disorders for years with its first clinical use dating back to 1959 for the treatment of acute amatoxin poisoning. According to Packer et al., it has been shown to play a role in mitochondrial dehydrogenase reactions. α-Lipoic acid reacts with reactive oxygen species and protects membranes by interacting with Vitamin C and enhancing intracellular glutathione, which may in turn recycle vitamin E. ALA may also exert pro-oxidant activities through a reduction of iron and has shown benefit in various oxidative stress models.

Product Characteristics

- **Produced organically in the body, occurs naturally in fatty-acids found in various foods (yeast, spinach, potatoes, organ meats, and others), used in oral solid dosages and IV**
- **No serious toxicity reported in clinical safety studies.** Nausea, vomiting, and vertigo reported in up to 10% of patients at doses of 1800 mg daily.
- **Cheap and relatively easy to manufacture**

Current Status

Medicinal use of alpha-lipoic acid has not yet been approved by the FDA but it is commonly used today to help treat diabetic neuropathy (shown to have a clinical benefit in reducing major symptoms and triglycerides levels). The FDA notes that although ALA is often compounded and used to treat pancreatic cancer, liver disease, and fibromyalgia, there is no convincing evidence of clinical activity. In addition, various clinical studies have shown that ALA has some benefit in body weight reduction (incl. antipsychotic drugs-related weight gain), anti-inflammatory effects in MS, anti-dementia or anti-Alzheimer's Disease properties, and various others but more clinical evidence is needed to support therapeutic efficacy in these indications.

COVID-19 Status

Alpha-lipoic acid is currently being reviewed in 2 clinical studies as a potential therapy for COVID-19.

Wu et al. found that the oxidative stress in host cells was an important factor in the infectivity of human coronavirus 229E and the glucose-6-phosphate dehydrogenase (G6PD) deficiency was another factor that enhanced human coronavirus 229E infection. It was reported that the addition of an antioxidant such as α-lipoic acid to G6PD-knockdown cells made the cells less susceptible to virus-induced cell death. In addition, Baur et al. found that ALA is an effective inhibitor of HIV-1 replication (over 90% reduction of reverse transcriptase activity could be achieved with 70 µg alpha-lipoic acid/ml). Thus, some researchers have hypothesized ALA as a potential therapy for COVID-19. Further, in a recent publication by McCarty et al., it was reported that phase 2 inducers (such as lipoic acid) may help to prevent/control RNA virus infections by amplifying the signaling functions of TLR7 and MAVS in evoking type 1 interferon production, thus boosting the type 1 interferon response to RNA viruses including influenza and coronavirus.

Source: Guggenheim Securities, LLC; FDA.gov.; Salehi et al.

Alpha-lipoic acid – Relevant Preclinical Data Summary

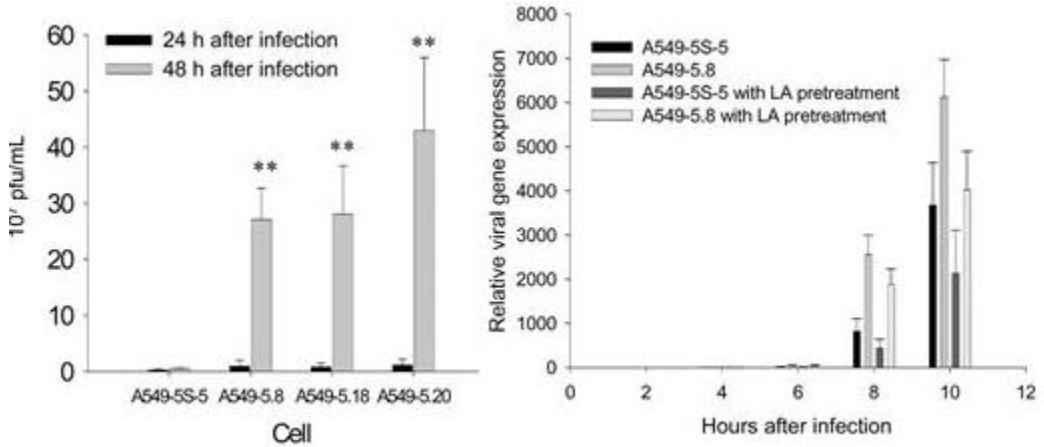
Although there are various data supporting a potential benefit in various polyneuropathies and hepatic disorders, the most clinically relevant data to COVID-19 is a study published by Wu et al. demonstrating that the addition of a potent antioxidant (i.e. α-lipoic acid) to G6PD-knockdown cells attenuated the increased susceptibility to Human coronavirus 229E infection.

Brief background:
Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common immune deficiencies in the world, which have been found to cause abnormal cellular redox, thus affecting cells other than red cells. Oxidative stress is known to affect viral proliferation and virulence. Human coronavirus (HCoV) 229E, recognized as a cause of the common cold and respiratory tract infections, is a large, enveloped RNA virus. Since pulmonary cells are under high oxidative stress and because HCoV 229E is a viral pathogen affecting pulmonary cells, Wu et al. investigated how oxidative stress affects HCoV 229E infections of the airway.

Summary of relevant results:
To evaluate whether ectopic application of antioxidants protects G6PD-knockdown cells from viral infection, α-lipoic acid, was applied in culture medium for 5h before virus infection. The viral gene expression in G6PD-knockdown cells pretreated with antioxidant was found to be lower than that in the untreated cells. A certain set of cells pretreated with antioxidant were 23% less susceptible to virus-induced cell death than control cells 48h after infection (MOI 0.1). Together, these data demonstrate the association between susceptibility to HCoV 229E infection and cellular redox status. This study shows, for the first time, that oxidative stress increases susceptibility of G6PD-deficient cells to viral infection. Importantly, these findings demonstrate that enhanced viral infection in G6PD-deficient cells is ameliorated by potent antioxidants, such as lipoic acid.

Viral particle production was higher in G6PD-knockdown A549 cells (A549–5.8, A549–5.18, and A549–5.20) than in control cells (A549–5S-5).

Viral gene (nucleocapsid) expression in cells pretreated with an antioxidant, lipoic acid (LA), was reduced in comparison to control cells as determined by quantitative polymerase chain reaction at 2, 4, 6, 8, and 10h after infection with HCoV 229E.



Source: Guggenheim Securities, LLC; Wu et al.

Ongoing Clinical Trials (China)

Alpha-lipoic acid is currently being evaluated in 2 trials in China.

Chinese Clinical Trial Registration/ trial link	Title	Enrollment	Sponsor	Primary Est. Completion
ChiCTR2000029851	A multicenter, randomized controlled trial for the efficacy and safety of Alpha lipoic acid (iv) in the treatment of patients of severe novel coronavirus pneumonia (COVID-19)	N=68	Zhongshan Hospital, Fudan University	03/10/2020
ChiCTR2000030471	Efficacy and safety of lipoic acid injection in reducing the risk of progression in common patients with novel coronavirus pneumonia (COVID-19)	N=394	Maoming People's Hospital	04/30/2020

Source: Guggenheim Securities, LLC; Chinese Clinical Trial Registry

Dipyridamole – First Affiliated Hospital of Guangzhou Medical University

Background and Mechanism

Dipyridamole (DIP) is an antiplatelet agent and acts as a phosphodiesterase (PDE) inhibitor that increases intracellular cAMP/cGMP.

Apart from the well-known antiplatelet function, DIP may provide additional therapeutic benefits to COVID-19 patients. Published studies [link], including clinical trials conducted in China, have demonstrated that DIP has a broad spectrum antiviral activity, particularly efficacious against the positive-stranded RNA viruses. Besides this, DIP also suppresses inflammation and promotes mucosal healing. As a pan-PDE inhibitor, DIP may prevent acute injury and progressive fibrosis of the lung, heart, liver, and kidney.

Product Characteristics

- **Oral tablets**

Current Status / Commentary

Currently Dipyridamole is not approved anywhere for any use.

COVID-19 Status

Preclinical research by Liu et al demonstrated that DIP possessed anti-HCoV-19 effects *in silico and in vitro*. In a VSV-induced pneumonia model, Liu et al also confirmed that DIP elicited potent antiviral immunity and significantly improved the survival rate.

In a retrospective analysis of a small clinical cohort, Liu et al found that DIP adjunctive therapy led to increased circulating lymphocyte and platelet counts and lowered D-dimer levels, and markedly improved clinical outcomes.

DIP is currently being evaluated in a Phase 4 randomized study in China sponsored by The First Affiliated Hospital of Guangzhou Medical University.

NCT ID / trial link	Title	Enrollment	Sponsor	Geography	Primary Est. Completion
ChiCTR2000030055	Multicenter study for the treatment of Dipyridamole with novel coronavirus pneumonia (COVID-19)	N = 460	The First Affiliated Hospital of Guangzhou Medical University	China	4/10/2020

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Dipyridamole – Relevant Data Summary

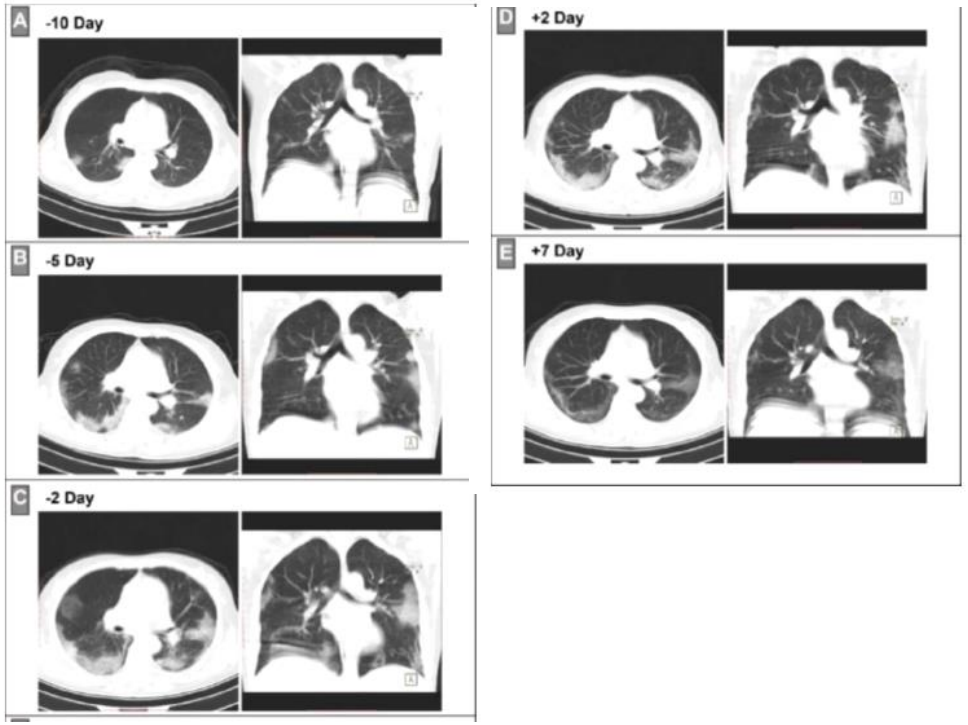
Table 2. Clinical outcomes of 27 enrolled patients			
	Severity of illness — no. (%)	**Outcomes (up to 2/26)**	**Total discharge — no. (%)**
Dipyridamole group (n=12)	Mild — 4 (33.3%)	4 discharged (100%)	7 (58.4%)
	Severe — 6 (50.0%)	3 discharged (50%) 2 in remission (33%)	
	Critical ill — 4 (33.3%)	1 in remission (50%) 1 death (2/09)	
Control group (n=10)	Mild — 4 (40.0%)	3 discharged (75%)	4 (40.0%)
	Severe — 4 (40.0%)	1 discharged (25%) 1 in remission (25%)	
	Critical ill — 2 (20.0%)	1 death (2/18)	

To evaluate DIP as a therapy to reduce the risk of hypercoagulability, 22 patients including 10 control patients and 12 patients who received DIP were recruited. Baseline characteristics of the two cohorts were similar.

Two weeks after initiation of DIP treatment, 3 of the 6 severe cases (50%) and all 4 of the mild cases (100%) were discharged from the hospital. One critically ill patient with extremely high levels of D-dimer and lymphopenia at the time of receiving DIP passed away. All other patients were in clinical remission. In comparison, the discharge and remission rates of the mild and severe cases were inferior in the control patients.

Before DIP treatment

After DIP treatment



All patients had chest CT scans and showed typical multiple patchy ground-glass shadows in the lungs before the treatment. In the DIP treated patients, the lesions had varied degree of absorption.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

RNAi Therapeutic – VIR / ALNY

Background and Mechanism

VIR Biotechnology and Alnylam are collaborating to develop and commercialize RNAi therapeutics that target COVID-19. The collaboration is focusing on siRNAs that target conserved regions of SARS-CoV-2 that Alnylam has recently discovered.

Current Status / Commentary

This program is currently in preclinical development.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

siRNA therapeutics – Sirnaomics

Background and Mechanism

Sirnaomic is developing RNAi-based prophylactics and therapeutics towards severe acute respiratory infection (SARI) caused by COVID-19. The company noted that it plans to develops multiple siRNA candidates.

iRNA prophylactics and therapeutics to treat SARS coronavirus, H5N1 influenza and other respiratory viral infections, with multiple animal models including non-human primate

Current Status / Commentary

Sirnaomics' programs are currently in preclinical development.

Sirnaomics has identified potentially potent siRNAs for targeting the viral genes critical for the viral infection and replication. Sirnaomics expects to develop multiple siRNA drug candidates.

Source: Company reports, clinicaltrials.gov, and Guggenheim Securities LLC Research

Sildenafil citrate

Background and Mechanism

Sildenafil citrate is a vasodilator & is the generic molecular name for the potentially better-known marketed drug Viagra (PFE). Sildenafil is a phosphodiesterase type 5 (PFE5) inhibitor and acts by prolonging the activity of cGMP. The drug is currently approved for use in erectile dysfunction (as Viagra), as well as pulmonary arterial hypertension (as Revatio [PFE]).

Current Status / Commentary

Sildenafil citrate is currently-approved for erectile dysfunction and pulmonary arterial hypertension.

Product Characteristics

- **There are three formulations: tablet, oral suspension, or IV injection.**
- **Cheap and relatively easy to manufacture**.

COVID-19 Status

Sildenafil citrate is being evaluated in 1 single site, investigator-sponsored trial in China.

Source: Guggenheim Securities LLC Research; clinicaltrials.org

Companies Mentioned

Abbott Laboratories (ABT, NEUTRAL, $70.75)	Clover Biopharmaceuticals (Private)	Mylan N.V. (MYL, CS, $14.93)
AbbVie, Inc. (ABBV, CS, $67.91)	Codagenix (Private)	Novacyt SAS (ALNOV-PAR, NC, €1.82)
AbCellera (Private)	CureVac (Private)	Novartis AG (NOVN-SWX, NEUTRAL, 74.56 CHF)
Allovir (Private)	Danaher Corporation (DHR, NC, $129.32)	Novavax, Inc. (NVAX, NC, $11.75)
Almirall SA (ALM-MCE, NC, €9.52)	Eli Lilly and Company (LLY, NEUTRAL, $121.94)	Pfizer Inc. (PFE, CS, $29.75)
Alnylam Pharmaceuticals, Inc (ALNY, BUY, $98.78)	Emergent BioSolutions Inc. (EBS, BUY, $54.72)	Pharmstandard (Private)
Altimmune, Inc. (ALT, NC, $3.43)	Enanta Pharmaceuticals, Inc. (ENTA, NC, $46.63)	Regeneron Pharmaceuticals, Inc. (REGN, BUY, $429.78)
Amneal Pharmaceuticals, Inc. Class A (AMRX, SELL, $3.49)	Etna Biotech (Private)	Rheonix Corporation (Private)
Apeiron Biologics (Private)	EUSA Pharma (Private)	Ridgeback Biotherapeutics (Private)
Arcturus Therapeutics Holdings, Inc. (ARCT, BUY, $15.76)	Evvivax (Private)	RNACure Biopharma (Private)
Ascletis Pharma, Inc. (1672-HKG, NC, 2.78 HKD)	ExpreS2ion Biotechnologies (Private)	Roche Holding AG (ROG-SWX, NC, 295.35 CHF)
AstraZeneca PLC (AZN-LON, BUY, £69.18)	FUJIFILM Holdings Corp (4901-TKS, NC, ¥4908)	Sanofi (SAN-PAR, BUY, €76.80)
Azidus Brasil (Private)	GeoVax Labs, Inc. (GOVX, NC, $0.21)	Shanghai Fosun Pharmaceutical (Group) Co., Ltd. Class H (2196-HKG, NC, 23.10 HKD)
BeiGene, Ltd. Sponsored ADR (BGNE, NEUTRAL, $121.84)	Gilead Sciences, Inc. (GILD, NEUTRAL, $69.66)	Sirnanomics (Private)
BioCryst Pharmaceuticals, Inc. (BCRX, NC, $2.01)	GlaxoSmithKline plc (GSK-LON, NEUTRAL, £14.896)	Sorrento Therapeutics, Inc. (SRNE, NC, $1.99)
BioFire Defense (Private)	Greffex (Private)	Stermirna Therapeutics (Private)
Biogen Inc. (BIIB, BUY, $284.98)	Heat Biologics, Inc. (HTBX, NC, $0.58)	Takeda Pharmaceutical Co. Ltd. (4502-TKS, NC, ¥3345)
BioNTech SE Sponsored ADR (BNTX, NC, $47.20)	Inovio Pharmaceuticals, Inc. (INO, NC, $6.68)	Takis Biotech (Private)
BravoVax (Private)	Jiangsu Famous Medical Technology Co (Private)	Teva Pharmaceutical Industries Limited Sponsored ADR (TEVA, NEUTRAL, $7.84)
Bristol-Myers Squibb Company (BMY, NEUTRAL, $49.35)	Johnson & Johnson (JNJ, CS, $119.40)	Thermo Fisher Scientific Inc. (TMO, NC, $271.68)
Cadila Healthcare Limited (532321-IN, NC, 264.05 INR)	Kamada Ltd (KMDA, NC, $5.52)	Tonix Pharmaceuticals Holding Corp. (TNXP, NC, $0.74)
CanSino Biologics, Inc. Class H (6185-HKG, NC, 112.20 HKD)	Laboratorios Gebro Pharma SA (Private)	Vaxart, Inc. (VXRT, NC, $1.68)
CAR-T (Shanghai) Biotechnology Co., Ltd. (Private)	Laboratorios Rubio SA (Private)	Vaxil Bio Ltd. (VXL-TSX, NC, 0.15 CAD)
Celltrion, Inc. (068270-KRX, NC, 183000 KRW)	Medicago (Private)	VBI Vaccines, Inc. (VBIV, NC, $0.88)
CEL-SCI Corporation (CVM, NC, $11.76)	Mesa Biotech (Private)	Vir Biotechnology, Inc. (VIR, NC, $30.75)
Cipla Limited (500087-IN, NC, 376.70 INR)	Moderna, Inc. (MRNA, NC, $27.13)	Wuxi Biologics (Cayman) Inc. (2269-HKG, NC, 102.50 HKD)

Source: FactSet priced as of 3/24/2020

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