COVID-19 Therapeutic Research and Development Landscape: Supplementary Download

Developed by L.E.K.'s Global Healthcare Insights Center (HIC)

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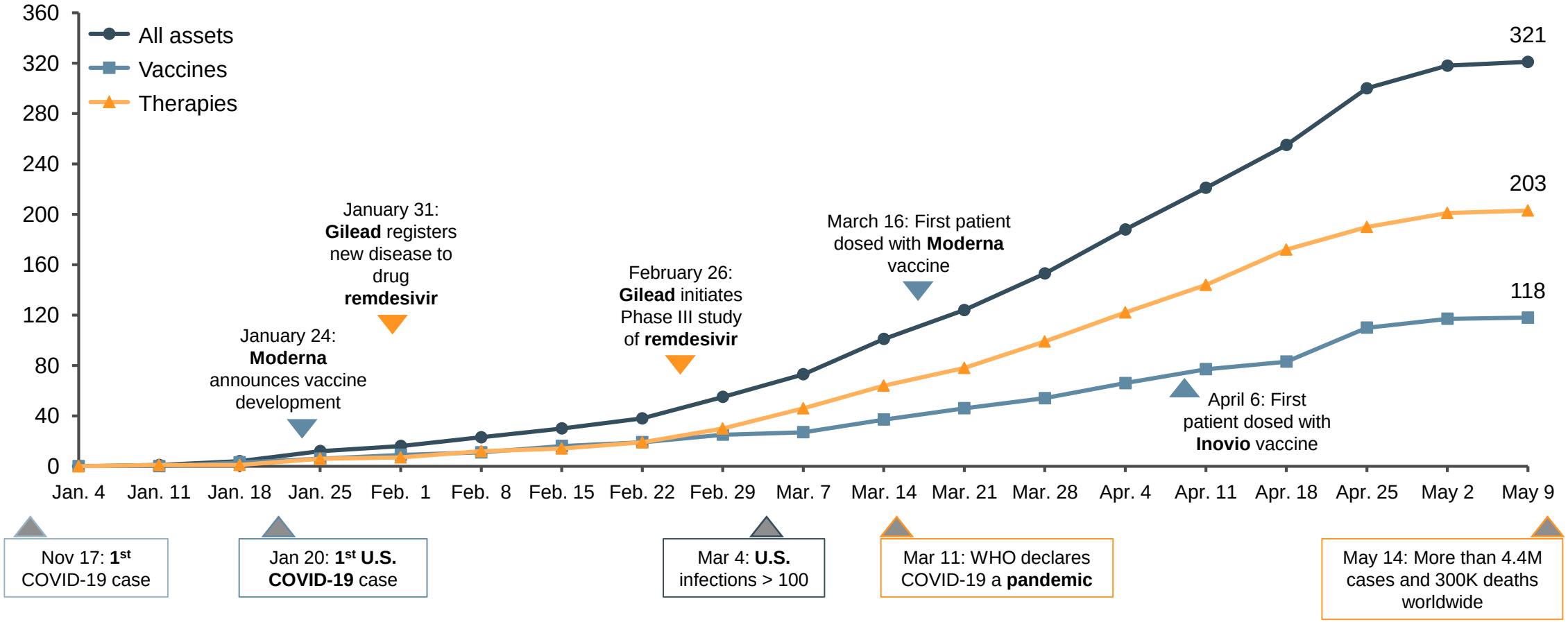
Contents of these materials:

- COVID-19's impact is first and foremost a global humanitarian crisis that has thrown us into uncharted territory. We at L.E.K. Consulting extend our heartfelt sympathies to all who are affected by this crisis around the world
- These materials provide additional asset-by-asset information on the therapeutic candidates in development for COVID-19 as a supplement to the *Executive Insights* published on our webpage
- The research and development (R&D) pipeline is evolving, with new assets in development and with both scientific and anecdotal data being refreshed on a daily basis; hence, certain perspectives may be out of date at the time of publishing

More than 300 individual assets are in development for COVID-19 worldwide, demonstrating the wide-ranging manner in which the biopharma industry has mobilized its response

Worldwide timeline of COVID-19 asset development start*
Number of assets (2020)



*Denotes the date that a new drug was added or new license reported on Pharmaprojects, press release dates were used for select assets not in Pharmaprojects
Sources: Pharmaprojects pull as of 5/12/2020; company press releases; L.E.K. research and analysis

Case study: Fujifilm's favipiravir

FUJIFILM
Value from Innovation

In-clinic:
Phase III (India)
Phase II (U.S.)

R&D commencement: February 2020
Humans dosed: ~2,000+
Funding disclosed: N/A
Therapeutics type: Repurposed antiviral

Asset overview

- Favipiravir is a selective inhibitor of the RNA polymerase involved in viral replication; animal studies have shown that it is effective against influenza as well as West Nile virus, yellow fever, foot-and-mouth disease and other viruses
- Favipiravir, which Fujifilm sells under the brand name Avigan, has been approved in Japan since 2014 to treat influenza and other viral strains that don't respond to other drugs and is being considered as a treatment for COVID-19

Development timeline

- In Japan, Phase III clinical trials are expected to conclude in June; according to the Ministry of Health, Labor and Welfare more than 2,000 people in Japan have been treated with favipiravir as part of clinical trials as of April 26, and the government has ordered 2 million treatment courses
- Japan is also shipping favipiravir to 43 countries for clinical trials with COVID-19 patients who have mild and moderate cases
- In the U.S., Fujifilm started Phase II trials in April with 50 people in three Massachusetts hospitals
- Glenmark Pharmaceuticals has received approval from the Drug Controller General of India to evaluate favipiravir in clinical trials to treat patients with COVID-19; Glenmark developed the drug's active pharmaceutical ingredients and formulations internally, and approximately 150 patients are expected to be enrolled in the study

Reasons for optimism

- Favipiravir has extensive late-stage clinical trials underway in multiple countries including the U.S. and Japan; the Japanese government has been a vocal proponent of the asset
- Fujifilm has partnered with the Japanese government and is in the process of securing additional raw material supply to boost production

Sources: *Chemical and Engineering News*; Clincial Trials Arena; CNBC; ClincialTrials.gov; L.E.K. research and analysis

Case study: Roivant's gimsimulab

ROIVANT SCIENCES

In-clinic: Phase III

R&D commencement: April 2020
Humans dosed: Up to 270
Funding disclosed: N/A
Therapeutics type: Repurposed antibody

Asset overview

- Gimsimulab is a monoclonal antibody administered intravenously that targets GM-CSF, a cytokine that is upregulated in severe COVID-19 patients, who either have or are at risk of developing acute respiratory distress syndrome (ARDS),* which has a 41% mortality rate
- Many hospitalized COVID-19 patients experience an overactive immune response consisting of cytokine dysregulations and increased inflammatory response leading to lung injury, ARDS and death; scientists believe that GM-CSF may contribute to clinical worsening of COVID-19 as GM-CSF is believed to be a key driver of lung hyperinflammation and operates upstream of other pro-inflammatory cytokines and chemokines

Development timeline

- Gimsimulab is a repurposed antibody that has been tested in numerous nonclinical and two clinical studies for rheumatoid arthritis, including a four-week Phase I study in healthy volunteers that concluded in February
- In April, Roivant announced the dosing of the first COVID-19 patient in the BREATHE Phase II clinical trial for the prevention and treatment of ARDS
- In addition to the first dosing at Temple University Hospital, dosing is expected to begin at Mount Sinai (NYC) and subsequent trial sites soon; trials are being supported by partnerships with Altasciences and Kinevant Sciences

Reasons for optimism

- Roivant's gimsimulab study for ARDS is the first for an anti-GM-CSF therapy initiated in severe COVID-19 patients
- Gimsimulab has demonstrated a favorable safety and tolerability profile based on data collected in previous nonclinical and Phase I studies

*COVID-19 may lead to ARDS in some patients
Source: Roivant website; L.E.K. research and analysis

Case study: Gilead's remdesivir

GILEAD
Creating Possible

In-clinic:
Phase III
EUA* granted 5/1/2020

R&D commencement: February 2020
Humans dosed: ~1,000
Funding disclosed: N/A
Therapeutics type: Repurposed antiviral

Asset overview

- Remdesivir is an investigational nucleotide analog with broad-spectrum antiviral activity, administered intravenously in a five- or 10-day dosing
- It has demonstrated in vitro and in vivo activity in animal models against MERS/SARS pathogens, which are coronaviruses and similar in structure to COVID-19
- Remdesivir makes growing chains of viral RNA terminate prematurely, thereby killing the virus and preventing replication
- Gilead has struck agreements with five generic manufacturers to help produce remdesivir for over 127 countries

Development timeline

- Remdesivir is a repurposed antiviral originally used for hepatitis C (in 2009) and then Ebola (in 2015); Gilead began COVID-19 work on remdesivir in February
- Gilead initiated two Phase III clinical trials to evaluate the safety and efficacy of remdesivir in adult COVID-19 patients after the Food and Drug Administration's rapid review and acceptance of Gilead's investigational new drug filing; these studies began enrolling patients in March, with the goal of enrolling ~1,000 patients
- There are also two ongoing remdesivir ongoing trials in China; the National Institute of Allergy and Infectious Diseases (NIAID) has initiated a Phase II double-blind trial for hospitalized COVID-19 patients; INSERM in France has also begun evaluating remdesivir among other treatment options

Reasons for optimism

- On May 1, the FDA officially granted EUA for remdesivir to treat COVID-19 in severe hospitalized patients; data showed remdesivir cut recovery time for hospitalized patients by 31%, and the mortality rate declined to 8% from 11% for those who received placebo (not statistically significant)
- The U.S. government will coordinate the distribution of remdesivir to hospitals with the highest need, beginning in early May

*Emergency use authorization
Sources: *The New York Times*; *FierceBiotech*; The Hill; Gilead website; L.E.K. research and analysis

Case study: Ascletis's ASC09 and AbbVie's ritonavir

In-clinic:
Phase II

R&D commencement: February 2020
Humans dosed: N/A
Funding disclosed: N/A
Therapeutics type: Novel antiviral

Asset overview

- ASC09, developed by Ascletis, was originally intended as an antiviral for HIV patients; clinical trials have demonstrated that ASC09 has a high genetic barrier to resistance compared with other approved protease inhibitors and strong antiviral activity
- Ritonavir, developed by AbbVie, is an HIV protease inhibitor that was initially developed as an independent antiviral agent but is now more commonly used as a booster of other protease inhibitors
- The combination of these two drugs is under investigation for COVID-19 due to their potential synergistic relationship

Development timeline

- In April, the ASC09/ritonavir fixed-dose combination received IND approval from the National Medical Products Administration (NMPA) as a HIV protease inhibitor; the effects of ASC09/ritonavir on COVID-19 are currently being investigated
- A number of clinical trials initiated in February are currently underway to evaluate the efficacy of ASC09/ritonavir on COVID-19 as well as to compare its efficacy with the combination of lopinavir/ritonavir

Reasons for optimism

- ASC09/ritonavir is a novel antiviral that has been shown through clinical trials to be safe and well tolerated

Sources: BioSpace; Drug Bank; ClincialTrials.gov; L.E.K. research and analysis

Case study: BioCryst's galidesivir

In-clinic:
Phase II

R&D commencement: April 2020
Humans dosed: ~60
Funding disclosed: ~$65 million
Therapeutics type: Repurposed antiviral

Asset overview

- Galidesivir is an RNA polymerase inhibitor that has shown broad-spectrum activity in vitro against more than 20 RNA viruses in nine different families; in animal studies, galidesivir has also demonstrated activity against a variety of serious pathogens, including Ebola, Marburg, yellow fever and Zika viruses
- Since September 2013, NIAID has supported BioCryst in developing galidesivir as a therapeutic for Ebola and Marburg viruses; since March 2015, Biomedical Advanced Research and Development Authority (BARDA) has supported BioCryst for the continued development of galidesivir as a potential treatment for filoviruses

Development timeline

- BioCryst has completed Phase I clinical safety and pharmacokinetics trials of galidesivir by both intravenous and intramuscular routes of administration in healthy subjects; the drug was shown to be safe and well tolerated
- In mid-April, BioCryst initiated a double-blind clinical study funded by the NIAID that will be conducted in Brazil under a U.S. IND application

Reasons for optimism

- Galidesivir's COVID-19 clinical trials for galidesivir are currently being funded by NIAID (NIH); historically, the drug's development has also been strongly supported and funded by both NIAID and BARDA, which may accelerate the approval process for the drug
- Galidesivir has shown antiviral activity against the MERS and SARS coronaviruses, suggesting potential for effectiveness against COVID-19

Sources: BioCryst; ClincialTrials.gov; GlobeNewswire; L.E.K. research and analysis

Case study: Apeiron's APN01 (formerly GSK2586881)

APEIRON BIOLOGICS

In-clinic: Phase II

R&D commencement: February 2020
Humans dosed: ~90*
Funding disclosed: N/A
Therapeutics type: Repurposed antiviral

Asset overview

- APN01 is a recombinant form of human angiotensin-converting enzyme 2 (rhACE2) that was developed by Apeiron Biologics for the treatment of acute lung injury (ALI), ARDS and pulmonary arterial hypertension (PAH)
- The drug was licensed in 2010 to GSK but was removed from GSK's pipeline in 2019 as part of a cut in its respiratory disease pipeline
- Apeiron Biologics is now evaluating APN01 for COVID-19; the drug is designed to imitate rhACE2 used by the virus to enter host cells and is believed to possess the potential to inhibit the COVID-19 infection and reduce lung injury

Development timeline

- In 2012, GSK conducted a Phase II clinical trial to determine GSK2586881's effect on ALI/ARDS, which was terminated early due to lack of patient improvement; an additional Phase II trial was conducted to evaluate the drug's effect on PAH
- In late February, Apeiron initiated a pilot study in Guangzhou with 24 severe COVID-19 patients but withdrew clinical trials prior to enrollment
- In April, Apeiron initiated Phase II clinical trials of APN01 for the treatment of COVID-19 in Austria, Germany and Denmark; the Austrian government is providing funding support for the trials in Austria

Reasons for optimism

- APN01 has a unique dual mode of action, as it has the potential to prevent the virus from entering cells while also reducing the harmful inflammatory reactions in the lungs and protecting against acute lung injury (ALI/ARDS)

*In previous non-COVID-19-related Phase I and Phase II trials
Sources: BioWorld; ClinicialTrials.gov.; GSK; Clinical Trials Arena; L.E.K. research and analysis

Case study: ImmuneMed's humanized virus-suppressing factor-variant 13 (hzVSF)

In-clinic:
Phase II

R&D commencement: March 2020
Humans dosed: ~24
Funding disclosed: N/A
Therapeutics type: Repurposed antiviral

Asset overview

- hzVSF was originally developed as a treatment for chronic hepatitis B and severe influenza, though it can be used for a wide range of viral diseases
- It is administered intravenously across multiple doses, with the number of doses varying depending on the severity of the infection and rate of recovery
- hzVSF is shown to inhibit inflammatory cytokine production, after administration in coronavirus-positive mice; specifically, there were significant reductions in IFN-gamma, MCP-1, IL-6 and TNF-alpha

Development timeline

- In late March, hzVSF was administered in South Korea to treat COVID-19 pneumonia patients; by that point, it had been administered in four hospitals in South Korea
- The Korean Ministry of Food and Drug Safety approved the use of hzVSF for COVID-19 treatment at Yonsei Hospital on March 27 for individual patients

Reasons for optimism

- ImmuneMed has said that hzVSF increases the healing power of cells to suppress viral replication and reduce excessive inflammation
- In late April, severe coronavirus patients (typically on ventilators/extracorporeal membrane oxygenation) were given hzVSF and experienced significant improvement during the trial period; the hzVSF was added to dosing once doctors realized that using only Kaletra (an HIV drug) wasn't effective

Sources: TrialSite News; BioSpace; L.E.K. research and analysis

Case study: Synairgen's interferon beta-1a (SNG001)

synairgen

In-clinic:
Phase II

R&D commencement: March 2020
Humans dosed: up to 100
Funding disclosed: $17 million
Therapeutics type: Repurposed antiviral

Asset overview

- Synairgen's interferon beta-1a (SNG001) was originally developed to treat chronic obstructive pulmonary disease (COPD); respiratory viral infections (common cold, flu) can gravely exacerbate infections in patients with lung disease and may be worsened by a lack of interferon beta production in the lungs
- Interferon beta is a naturally occurring protein that initiates antiviral defenses in humans; in vitro models have shown that interferon beta protects lung cells of COPD patients when they have viruses that cause worsening of COPD
- SNG001 is a specific formulation of the interferon beta that is delivered to the lungs through a nebulizer

Development timeline

- In March, Synairgen received expedited authorization in the U.K. to conduct a trial of SNG001 in COVID-19 patients; the company is working with the NIHR Respiratory Translational Research Collaboration for the trials
- The trial aims to target older patients and people with specific comorbidities (heart/lung diseases) who are at greater risk of developing a severe or fatal form of COVID-19; by late March, Synairgen had begun to dose COVID-19 patients with SNG001

Reasons for optimism

- Asset is already widely used with an understood risk profile as an injectable for multiple sclerosis; Synairgen has already tested its inhaled version with 200 asthma patients experiencing cold/flu infections, which has shown improvements in lung function
- If Synairgen's hypothesis is correct, and COVID-19 has evolved mechanisms that suppress interferon beta production, then SNG001 via nebulizer into the lungs could reduce viral replication and cell damage

Sources: Synairgen website; Pharma Phorum; TrialSite News; L.E.K. research and analysis

Case study: RedHill's opaganib

In-clinic:
Phase II

R&D commencement: April 2020
Humans dosed: Up to 60
Funding disclosed: N/A
Therapeutics type: Repurposed antiviral

Asset overview

- Opaganib is a proprietary sphingosine kinase-2 (sk2) selective inhibitor that is administered orally and has anti-cancer, antiviral and anti-inflammatory effects
- sk2 is a lipid kinase that catalyzes formation of S1P, which promotes cancer growth and other proliferation and pathological inflammation
- RedHill acquired Opaganib from Apogee Biotechnology in March 2015, which had already completed successful preclinical trials with Opaganib in oncology and GI-inflammation, and a Phase I study of advanced tumor cancer patients

Development timeline

- In mid-April, RedHill submitted its IND for opaganib treatment of COVID-19 to the FDA, following preliminary discussions with the FDA on study design
- A U.S. Phase II trial aims to evaluate the safety and efficacy of opaganib with ~60 hospitalized COVID-19 patients
- In late April, data from Israel showed that six patients treated with opaganib experienced measurable clinical improvement; this includes decreased requirement of supplemental oxygen, higher lymphocyte counts and decreased C-reactive protein

Reasons for optimism

- Several preclinical studies demonstrate the potential role of sk2 in the replication of RNA viruses similar to coronaviruses; opaganib inhibits sk2 and therefore potentially blocks viral replication and pathological inflammation
- RedHill's medical director is encouraged by the findings from the Israel study, which showed improved outcomes in severe COVID-19 patients

Sources: RedHill website; European Pharmaceutical Review; L.E.K. research and analysis

Case study: Ridgeback Biotherapeutics and DRIVE's EIDD-2801

RIDGEBACKBIO

DRIVE
INFECTIOUS INNOVATION

In-clinic:
Phase I

R&D commencement: April 2020
Humans dosed: N/A
Funding disclosed: N/A
Therapeutics type: Novel antiviral

Asset overview

- EIDD-2801 is an oral antiviral that prevents the replication of SARS-CoV-2, the virus that causes COVID-19, and has shown efficacy against other coronaviruses (e.g., SARS-CoV, MERS-CoV) in animal models; EIDD-2801 also has broad spectrum activity against a number of diseases including influenza, chikungunya, Ebola and equine encephalitis
- The drug was developed by Drug Innovation Ventures at Emory (DRIVE) LLC, wholly owned by Emory University, and was exclusively licensed to Ridgeback Biotherapeutics in March 2020

Development timeline

- In early April, the FDA approved DRIVE's IND application for EIDD-2801, enabling the company to initiate human clinical trials
- EIDD-2801 has also received clearance by the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) to begin human testing; Ridgeback commenced Phase I in the U.K. on Friday April 10

Reasons for optimism

- EIDD-2801's potency against multiple coronaviruses and its oral bioavailability highlight its potential utility as an effective antiviral against SARS-CoV-2 and other future coronaviruses
- There is also potential for EIDD-2801 to be used as either a prophylactic or a therapeutic for SARS-CoV-2; used as a prophylactic, EIDD-2801 prevented severe lung damage, reduced the viral load and resulted in weight loss in mice when administered within 12-48 hours of infection — the window is expected to be longer in humans

Sources: Emory University; BioSpace; Drug Target Review; ClincialTrials.gov; L.E.K. research and analysis

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