

THE COVID-19 PANDEMIC AND HAEMOGLOBIN DISORDERS

VACCINATIONS & THERAPEUTIC DRUGS

*An Informational Guide
from the
Thalassaemia
International Federation
(TIF)*



**THALASSAEMIA
INTERNATIONAL
FEDERATION**

*Prepared by:
Dr Androulla Eleftheriou,
Executive Director, TIF*

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Introduction

It is important to note that there are currently no FDA¹ or EMA²-approved or even recommended agents for the treatment of the novel coronavirus (COVID-19), for which the World Health Organization (WHO) declared as pandemic on Wednesday 11th of March 2020. Any agent being used at this time is being administered in an experimental setting under controlled conditions.

Thalassaemia International Federation (TIF) has made an effort to compile a list of studies/clinical trials for treatment and vaccines, which is by no means exhaustive as this situation is extremely labile and research in this area is dramatically intensified. New information is anticipated to be added to this guide which is prepared exclusively for TIF's global thalassaemia community.

The viral genome was mapped very soon as from early January 2020 and shared globally.

In February 2020, the WHO published an overview of the potential therapeutic candidates for the treatment of COVID-19. The document outlines 76 regimens that have been proposed (as of February 17, 2020) for the treatment of patients infected with the virus. Thirty-eight of these candidates are in the preclinical state with minimal information available on their proposed mechanism, uses, doses routes, or planned trials. Sixteen of the remaining regimens contain an interferon-based product. The rest include a variety of antimicrobials, corticosteroids, convalescent plasma, and biologics.

The Director-General of the WHO, Mr Tedros Adhanom, stated on the 10th of April 2020, that more than 70 countries have joined WHO's trial to accelerate research on effective treatments and 20 Institutions and companies 'are racing to develop a vaccine'. The Director-General will be soon announcing an initiative for the accelerated development and equitable distribution of vaccines.

Global research and innovation forum: towards a research roadmap

On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

¹ [Food and Drug Administration \(FDA\)](#)

² [European Medicines Agency \(EMA\)](#)

World scientists on COVID-19 met at the World Health Organization's Geneva headquarters from 11 to 12 February 2020 to assess the current level of knowledge about the new virus, agree on critical research questions that need to be answered urgently, and ways to work together to accelerate and fund priority research that can contribute to curtail this outbreak and prepare for future outbreaks.

- 2019 Novel Coronavirus: Global Research and Innovation Forum: Towards a Research Roadmap/report
- 2019 Novel Coronavirus: Overview of the state of the art and outline of key knowledge gaps/slides
- A coordinated Global Research Roadmap

Vaccines

An international randomised trial of candidate vaccines against COVID-19, 19th April 2020

This large, international, randomized controlled clinical trial is designed to enable an expeditious, agile and concurrent evaluation of the benefits and risks of multiple candidate preventive vaccines against COVID-19 at international sites with sufficient COVID-19 attack rates. Different candidate vaccines may be available or suitable to enter the trial at different times; for each candidate vaccine, the primary efficacy results are expected within 3-6 months of the vaccine entering the trial.

The trial will rapidly enroll and individually randomize very large numbers of adult participants in many different populations. Each participant will be contacted weekly for information as to whether any potentially relevant symptoms have arisen, with laboratory testing triggered if the report suggests COVID-19. By using a shared placebo/control group and a common Core protocol to evaluate multiple candidate vaccines in the trial, resources allocated to the evaluation of each candidate vaccine are judiciously saved while a high standard of scientific rigor and efficiency is ensured.

The trial is powered to provide sufficient evidence of safety and vaccine efficacy against COVID-19 to support decision-making about global vaccine.

VACCINATIONS & THERAPEUTIC DRUGS

Moreover, a survey by Genetic Engineering & Biotechnology News (GEN) reveals: 35 active drug development programs in North America, Europe, and China. Companies involved range from pharma giants like GlaxoSmithKline and Sanofi, to small and large biotechs such as Moderna and Gilead Sciences. Gilead has already begun clinical trials in China where 234 clinical trials are registered (Chinese Clinical Trial Registry) 50% of which (105), of which 85 registered studies focus on treatments for COVID-19.

Many of these are included in the 60 studies listed in ClinicalTrials.gov whose descriptions include the term COVID-19, as well as the 7 studies whose descriptions include SARS-CoV-2. The U.S. website lists 331,715 trials in 209 countries.

China published Guidelines for clinical studies of drugs and vaccines intended to combat the deadly viral outbreak giving priority to drugs already marketed and whose efficacy has been proven in animal and in vitro studies.

In all the above studies and programmes, considerable effort is placed on repurposing existing drugs and assessing their effectiveness and safety in addressing COVID-19 while at the same time there is a plethora of drug developers, as seen in GEN's A-List of top 35 treatments under development and/or clinical study for COVID-19.

There are 412 published articles in the PubMed (a free full-text archive of biomedical and life sciences journal) and 312 clinical trials recruited at clinicaltrials.gov for 2020. "A global war of pharmaceutical industry and countries" with interest of over 1 trillion dollars always declaring of course "no conflict of interest".

WHAT IS MOST NEEDED TODAY, MORE THAN EVER IS:

A strong international co-ordination and co-operation is needed between the pharmaceutical industry to develop vaccines, regulatory authorities, policy makers, funders, public health agencies and governments to ensure that vaccines candidate for clinical trials would be manufactured in sufficient quantities and be accessible to all.

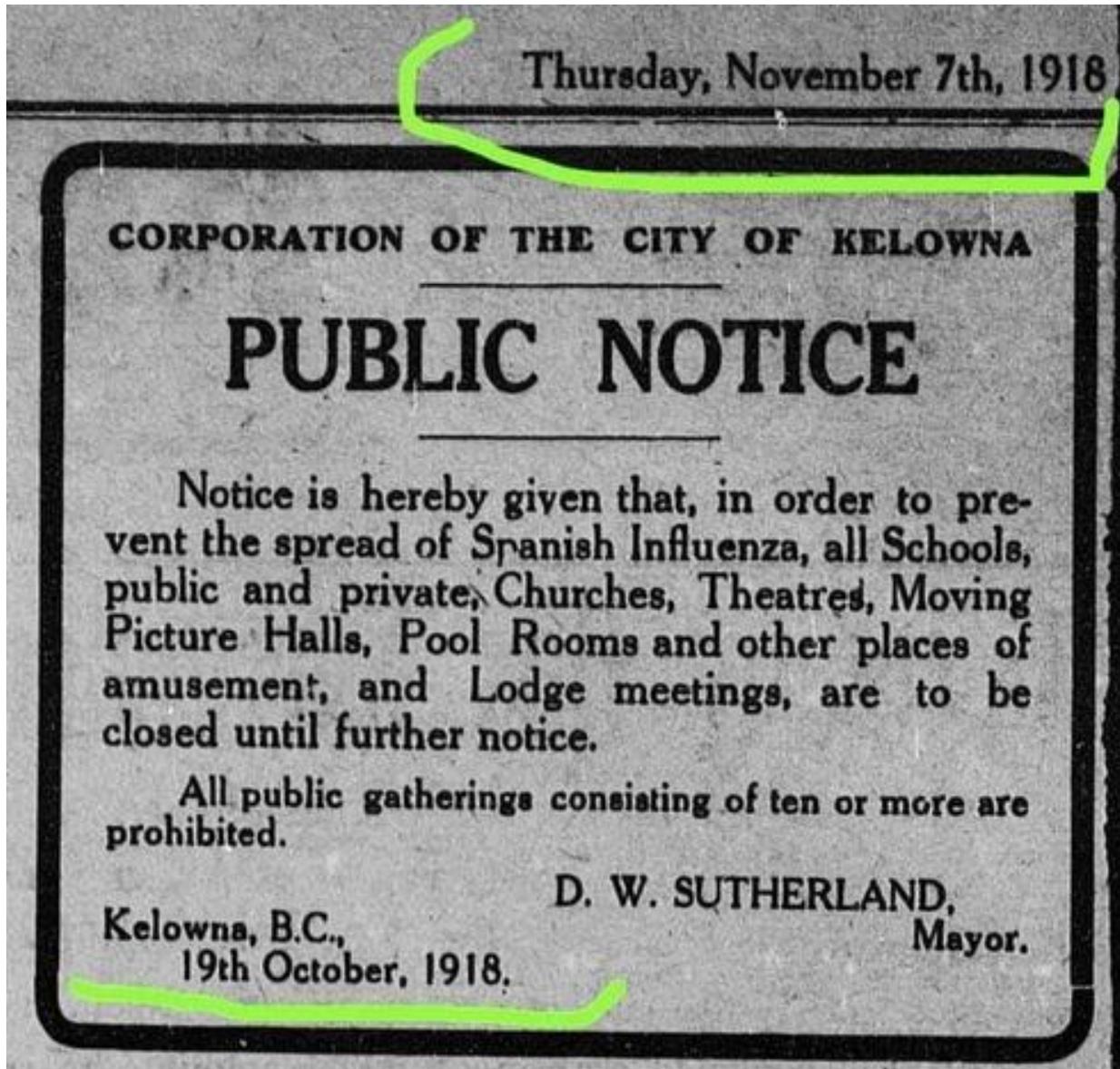
Earlier this month Microsoft founder and billionaire philanthropist Bill Gates issued an urgent call for world leaders to unite and start planning how vaccines will be manufactured and distributed now, to avoid a potentially deadly delay in delivering the treatment further down the line.

“We aren’t sure which vaccines will be the most effective yet, and each requires unique technology to make,” he said.

“That means nations need to invest in many different kinds of manufacturing facilities now, knowing that some will never be used. Otherwise, we’ll waste months after the lab develops an immunization, waiting for the right manufacturer to scale up.”

The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic.

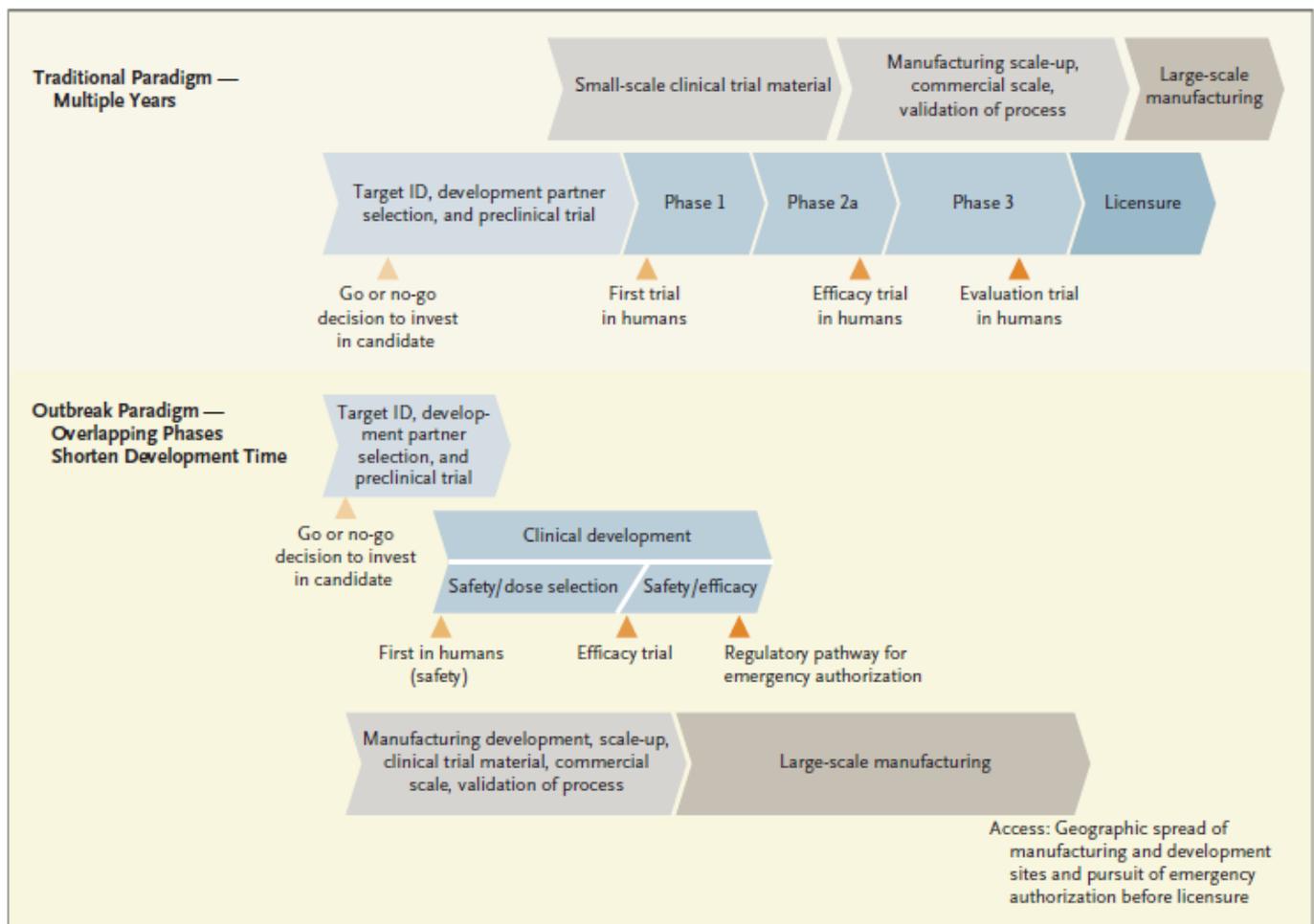
Measures during Spanish Influenza Pandemic



Candidate Vaccinations and Therapeutic Drugs

Below is a catalogue of the prospective vaccinations and therapeutic drugs listed by their developer and a short description.

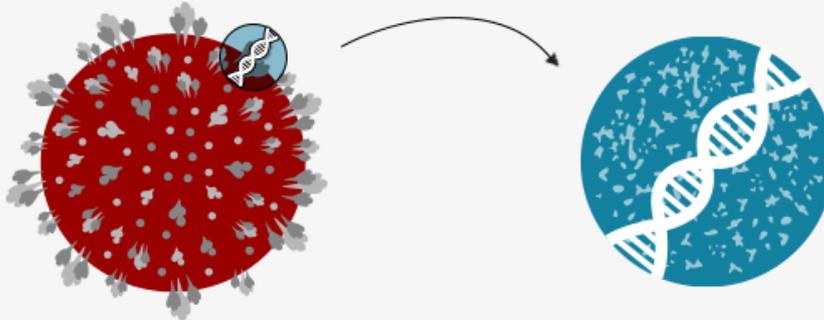
VACCINATIONS



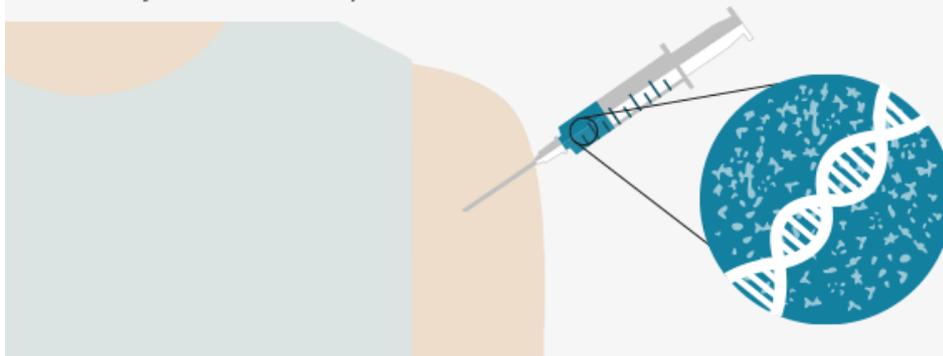
New England Journal of Medicine - Perspective, Developing Covid-19 Vaccines at Pandemic Speed

How coronavirus vaccine will work

Scientists have taken genes for the spike protein on the surface of coronavirus, and put them into a harmless virus to make a vaccine

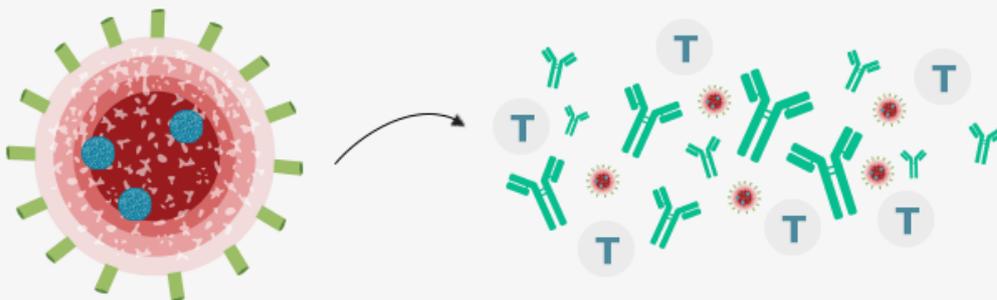


This is injected into the patient

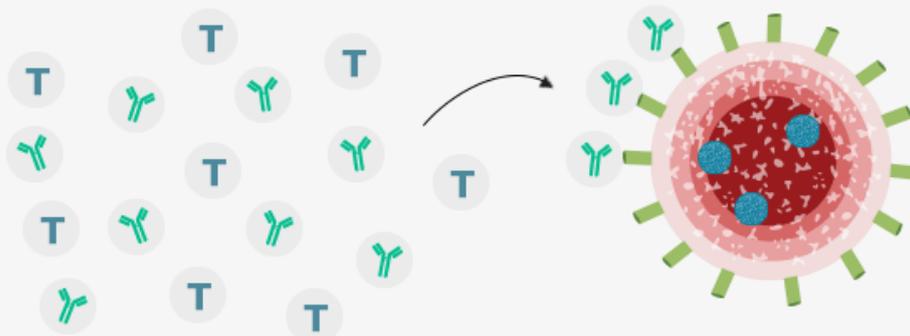


The vaccine enters cells, which then start to produce the coronavirus spike protein

This prompts the immune system to produce antibodies and activate killer T-cells to destroy infected cells



If the patient encounters coronavirus again, the antibodies and T cells are triggered to fight the virus



1. **AJ Vaccines**

AJ Vaccines has launched the development of a vaccine against COVID-19. The company will use the latest technology to develop antigens that can mimic the native structures of the virus. The vaccine will be capable of inducing a strong immune response in the body thereby protecting against the infection. As of the beginning of May the development is still at a preclinical stage.

2. **Altimune**

Single-dose, intranasal vaccine designed to provide systemic immunity

Vaccine based on Altimune's proprietary platform vaccine technology, which the company applied in developing NasoVAX, the company's influenza vaccine candidate that showed positive Phase IIa results.

Altimune said February 28 that it completed the design and synthesis of the vaccine, and was advancing it toward animal testing and manufacturing. Clinical testing of the vaccine, it was announced could start in the third quarter. The company also said it was "actively engaged in discussions with a number of potential partners."

3. **BioNTech and Pfizer**

BNTX, -4.44% COVID-19 candidate vaccine, was developed by BioNTech and supported by Pfizer. 360 patients in the U.S. had started to receive the first doses of the vaccine as of May 5. Dosing in 200 participants in the German trial began April 23. The vaccine uses a gene-based technology, messenger RNA, which has an advantage as it can move faster into clinical trials

The first round of trial data are expected in May or June, with the vaccine candidate moving into "expanded trials that could allow emergency use or accelerated approval coming in the fall, possibly October."

4. **CanSino Biologics and the Beijing Institute of Biotechnology**

Adenovirus type 5 vector-based recombinant COVID-19 vaccine, Ad5-nCoV, which has entered Phase 2 clinical trials in China. The decision to go forward was based on the preliminary safety data of the phase 1 clinical trial.

The study is designed to evaluate the immunogenicity and safety of the Ad5-nCoV vaccine—which encodes for a full-length spike (S) protein of SARS-CoV-2. The target is to enrol 500 participants, with 250 of the subjects to receive a middle-dose vaccine group, 125 subjects to receive a low-dose and 125 subjects in the placebo group. They will investigate the immunogenicity at days 0, 14, 28 and 6 months after vaccination. Results are not yet known.

5. Clover biopharmaceutical & GSK

The vaccine is being developed based on the trimeric s protein (S-TRIMER) of the COVID-19 virus which is responsible for binding with the host cell causing a viral infection. Clover scientists started designing the viral spike (S)-protein construct and completed its gene synthesis. The vaccine has been produced in February in a mammalian cell culture. A highly purified form is expected for pre-clinical studies.

Clover and GSK announce research collaboration to evaluate coronavirus COVID-19 S-Trimer vaccine. GSK will provide Clover with its pandemic adjuvant system for further evaluation of S-Trimer in preclinical studies.

6. CureVac

mRNA-based vaccine

Vaccine applying CureVac's mRNA vaccine development platform

CureVac and the public-private Coalition for Epidemic Preparedness Innovations (CEPI) are collaborating to develop a vaccine against SARS-CoV-2, the partners said January 31, extending their existing partnership to develop a rapid-response vaccine platform. CEPI has committed up to \$8.3 million in additional funding for accelerated development, manufacturing, and clinical tests. CEPI CEO Richard Hatchett said the Coalition and CureVac aspire to bring the pathogen's gene sequence to a vaccine candidate for clinical testing "within a few months."

The EU Commission has offered up to €80 million of financial support to CureVac a vaccine developer from Tübingen, Germany, to scale up development and production of a vaccine against the Coronavirus in Europe

7. Generex Biotechnology

Generex Biotechnology Corporation has been working to develop a peptide vaccine against the new coronavirus SARS-CoV-2 using the company's proprietary and patented li-Key immune system activation technology. The li-Key ensures potent activation of CD4+ T cells, which in turn facilitates antibody production to ward off infection. This li-Key modification can be applied to any protein fragment of any pathogen to increase the potency of immune stimulation.

Generex said February 27 it has received a contract from the China Technology Exchange, Beijing Zhonghua Investment Fund Management Co. Ltd., Biology Institute of Shandong Academy of Sciences, and Sinotek-Advocates International Industry Development (Shenzhen) Co. Ltd. to develop a li-key vaccine. Generex said it would receive \$1 million upfront to initiate project work in the U.S., a \$5 million licensing fee for the li-Key technology, payment by the Chinese consortium for all costs and expenses related to the development of a COVID-19 vaccine, and a 20% royalty on each dose of vaccine produced.

The intention is to conduct Clinical Trial with Lead li-Key/SARS-COV-2 Peptides, to evaluate safety & immunogenicity (DTH Assay) and then to proceed to commercial manufacturing & distribution in 5 to 9 months

GSK agreed to provide Clover with its pandemic adjuvant system for further evaluation of S-Trimer in preclinical studies, the companies said February 24, under a research collaboration. GSK reasons that Clover could rapidly scale-up and produce large-quantities of a new coronavirus vaccine since it has one of the largest in-house, commercial-scale cGMP biomanufacturing capabilities in China.

8. Heat Biologics

Heat Biologics has announced plans to develop a vaccine to treat or prevent coronavirus infection using its proprietary gp96 vaccine platform. The technology is capable of

reprogramming live cells to produce antigens that can bind to the gp96 protein and generate an immune response against those antigens. The company is finalizing completion of the vaccine and plan to commence preclinical testing this spring.

9. iBio and Beijing CC-Pharming

Plant-derived vaccine to be manufactured using iBio's FastPharming System™ iBio is hoping its technology can help accelerate manufacturing and scale up for a vaccine which the company is developing for COVID-19 and has partnered with Beijing CC-Pharming to test the vaccine in China. Plant-based production saves months in initial setup time compared with traditional pharma manufacturing methods.

The two companies on February 3 disclosed plans to develop and test the COVID-19 vaccine, combining the vaccine R&D experience (including work on the MERS-coronavirus), in a rapid design of manufacturing processes for biopharmaceutical production in plant-based expression systems. If successful, the research will deliver product candidates for production at iBio's *FastPharming* Manufacturing Facility, built in 2010 with funding from the Defense Advanced Research Projects Agency (DARPA), to establish facilities capable of rapid delivery of medical countermeasures in response to a disease pandemic.

10. ImmunoPrecise Antibodies

Vaccines and coronavirus-neutralizing antibodies

Prophylactic (i.e. vaccine) and therapeutic compounds (i.e. antibodies) using ImmunoPrecise's proprietary discovery platforms (including B Cell Select™ and DeepDisplay™) and ImmunoPrecise subsidiary Talem Therapeutics' access to the transgenic animal platform OmniAb® for direct generation of human antibodies.

The company has updated its research efforts and noted that it will be using the PolyTope mAb Therapy™ and EVQLV's artificial intelligence platforms to develop a COVID-19 therapy.

ImmunoPrecise announced its commitment to finding COVID-19 treatments on February 20, saying it had designated Ilse Roodink, PhD, chairwoman of Talem's scientific committee, as its Coronavirus Global Project Leader.

11. Imperial College Londo

Researchers at the Imperial College have developed a candidate which, when injected, will deliver the genetic instructions to muscle cells to make the SARS-CoV-2 spike surface protein. This should provoke an immune response and create immunity to the virus.

The team, led by Professor Robin Shattock from Imperial's Department of Infectious Disease, has been testing the candidate in animals since early February.

Clinical trials are expected to begin in June and the team will look to recruit healthy adults to test the vaccine.

Results could be available as soon as September.

12. Inovio Pharmaceuticals and Beijing Advaccine Biotechnology

The investigational DNA immunotherapy, INO-4800 (GLS-5300) is being developed by Inovio in partnership with GeneOne Life Science. It is delivered as vaccine intramuscularly, using the Celectra® (electroporation) delivery device.

The vaccine was well-tolerated and demonstrated high immune responses, when previously used against the MERS-CoV with high response in 94% of patients in the early-stage clinical trial in July 2019. It also generated broad-based T cell responses in 88% of the subjects.

The company stated pre-clinical testing for the SARS-CoV-2 virus. The development is supported by a \$9 million grant from the Coalition for Epidemic Preparedness Innovations (CEPI). Also, the company has received a \$5 million grant from the Bill & Melinda Gates Foundation to accelerate the testing and development of the Celectra® delivery device for the intradermal delivery of INO-4800. Phase 1 trial has started this month (April), in 40 volunteers. INO-4800 Phase 2/3 U.S. clinical trial being prepared to start this summer, according to a report from the company on 30th April. The company has entered into an agreement to expand its manufacturing partnership with the German contract manufacturer Richter-Helm BioLogics GmbH & Co. KG, to support large-scale manufacturing of INOVIO's investigational DNA vaccine, with plans to produce one million doses of INO-4800 by the end of 2020.

13. Integral Molecular

Integral Molecular has launched a vaccine programme using its two technology platforms including Shotgun Mutagenesis Epitope Mapping and the Membrane Proteome Array. The technologies will help in understanding the human immune response to the coronavirus and isolate the cellular receptors that enable the virus to spread quickly. SARS-CoV-2 reporter virus particles are designed to be antigenically identical to wild-type viruses but with a modified genome that expresses a convenient optical reporter gene (GFP or luciferase) upon cellular infection.

The Shotgun technology helps in identifying more than 1,000 binding sites for antibodies, while the Membrane Proteome Array technology is capable of identifying the receptors through which viruses infect cells.

The company is providing access to free SARS-CoV-2 RVP trial samples to vaccine developers to support COVID-19 research

14. Janssen Pharmaceutical Cos. (Johnson & Johnson)

An experimental vaccine is under development and human trials are expected to start in September. On March 30, the company stated that it had identified a lead vaccine candidate, and is scaling up its vaccine manufacturing capabilities aiming to put its lead vaccine candidate in a Phase 1 clinical trial in September.

15. LineaRx (Applied DNA Sciences) and Takis Biotech

Linear DNA vaccine

To be based on PCR-produced linear DNA designed to induce antibodies that can neutralize SARS-CoV-2

The PCR technology offers several advantages including high purity, increased production speed, and absence of antibiotics and bacterial contaminants. Further, the vaccine gene

developed through this technology can be effective without being inserted into the patient's genome.

The design for four DNA vaccine candidates is expected to be produced using the PCR technology for carrying out animal testing. The design of one of the vaccine candidates is based on the entire spike gene of the coronavirus, while the remaining are designed based on the antigenic portions of the protein.

LineaRx, a majority-owned subsidiary of Applied DNA Sciences of Stony Brook, NY, and Rome-based Takis Biotech said February 7 they have formed a joint venture to develop the preclinical vaccine using PCR-based DNA manufacturing technology. No commercial partner to take the coronavirus vaccine to market has been identified, the companies said.

16. Medicago

The company is developing a vaccine against SARS-CoV-2 and is partly funded by the Canadian Institutes of Health Research (CIHR).

Medicago expects to initiate human trials by this summer (July/August 2020) with the objective of completing the development program and submitting a dossier to authorities by the end of next year (November 2021). The vaccine should be available after approval from respective regulatory authorities.

17. MIGAL Research Institute

A newly formed Israeli company working to develop a vaccine for the novel coronavirus based on research by scientists at the Migal Galilee Research Institute secured \$12 million in an investment round led by Israeli crowdfunding venture investment platform OurCrowd.

The scientists had been working for four years to develop a vaccine against IBV (Infectious Bronchitis Virus), which affects the respiratory tract, Avian coronavirus Infectious Bronchitis Virus (IBV) vaccine. This vaccine has been modified to treat COVID-19. The IBV vaccine was developed after 4 years of research and has high genetic similarity to the human coronavirus. The Institute modified genetically the vaccine to treat COVID-19 and will be available in the oral form. Migal believes that its proposed oral (mucosal) vaccination technology can be ready for testing recently.

The company is in talks with major strategic partners able to manufacture at high volume and distribute globally.

18. Modern and Vaccine Research Centre

Novel lipid nanoparticle (LNP)-encapsulated mRNA vaccine (mRNA-1273) against the COVID-19 encoding for a prefusion stabilized form of the Spike (S) protein.

Moderna said February 24 that it shipped the first batch of mRNA-1273 to the NIH's National Institute of Allergy and Infectious Diseases (NIAID) for use in a planned Phase I study in the U.S. The primary aim of the Phase I open-label, dose-ranging trial study (NCT04283461), which had yet to recruit patients at deadline, is to evaluate the safety and reacto-genicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults. Moderna designed the vaccine in collaboration with investigators at the NIAID Vaccine Research Center (VRC).

The first patient was dosed on March 16 and Phase I is still ongoing and is expected to conclude in June 1. Participants will be followed for one year.

An unusual aspect is that this vaccine has NOT BEEN TESTED in laboratory animals as is the rule. Phase 2 trials are expected to start this spring, since Moderna has received the green light to initiate the trial. However, Moderna is pushing forward with manufacturing the potential vaccine, as early as July, hoping that it proves safe for humans and effective against the coronavirus.

19. Novavax

Vaccines designed to apply company's proprietary recombinant protein nanoparticle technology platform to generate antigens derived from the coronavirus spike (S) protein. Novavax said it expects to utilize its proprietary saponin-based Matrix-M™ adjuvant with COVID-19 vaccine candidates to enhance immune responses.

Novavax developed a novel Middle East Respiratory Syndrome (MERS) coronavirus vaccine candidate in 2013, post the identification of the first MERS coronavirus ((MERS-CoV) in Saudi Arabia in 2012. It is a crucial target for vaccine development by the Coalition for Epidemic Preparedness Innovations (CEPI) and is a priority disease for the World Health Organisation (WHO).

Phase 1 clinical trials are scheduled to start in mid-May. The first phase of the placebo-controlled study will enrol 130 healthy adults and the first round of data from that study is expected in July.

20. Oxford University

ChAdOx1 nCoV-19 vaccine. This is a more so-called platform technology which is used to make vaccines against many different diseases.

The Oxford University, supported by the UK Ministry of Health (announced April 21) has already started clinical trials in humans in April 2020.

A £52.5 million funding has also been announced by the UK Health Secretary for another vaccine trial at London's Imperial University due to begin in June.

The vaccine is an adenovirus vaccine vector (ChAdOx1) and was developed at Oxford's Jenner Institute. It has recently received further £20 million funding from the UK Government almost all of it expected to be spent on the clinical trial development programme. Prof Andrew Pollard, Chief Investigator, said that they expected to produce a million doses as early as September (ahead of the 12-18 month timeline quoted by experts around the world).

It was chosen as the most suitable vaccine for COVID-19 as it can generate a strong immune response from one dose, but is not a replicating virus.

The Oxford University team's experimental product, called "ChAdOx1 nCoV-19", is a type of immunisation known as a recombinant viral vector vaccine and is just one of at least 70 potential Covid-19 candidate shots under development by biotech and research teams around the world.

The vaccine was chosen as the most suitable vaccine technology for the virus as it can generate a strong immune response from one dose, said the team.

This means that the vaccine won't cause an ongoing infection in the vaccinated person, and also makes it safer to give to children, the elderly and anyone with a pre-existing condition such as diabetes.

Who is the vaccine being tested on?

The trial will be split into three main Phases:

1. Phase 1 will involve 510 healthy participants, aged 18 to 55, who will either receive the ChAdOx1 nCoV-19 vaccine or a control injection for comparison. At the start of the trial we will also recruit a separate small group of 10 volunteers who will receive 2 doses of ChAdOx1 nCoV-19 four weeks apart.

What does the study involve?

Up to 1102 participants will be recruited across multiple study sites in Oxford, Southampton, London and Bristol. These participants will be randomly allocated to receive either the ChAdOx1 nCoV-19 vaccine or a licensed vaccine (MenACWY) that will be used as a 'control' for comparison. This study is currently in progress and results are expected in June. If favourable a vaccine should be available for the public in September.

What is the MenACWY vaccine?

The MenACWY vaccine is a licensed vaccine against group A, C, W and Y meningococcus which has been given routinely to teenagers in the UK since 2015 and protects against one of the most common causes of meningitis and sepsis. This vaccine is also given as a travel vaccine for high risk countries.

The MenACWY vaccine is being used as an 'active control' vaccine in this study, to help us understand participants' response to ChAdOx1 nCoV-19. The reason for using this vaccine, rather than a saline control, is because we expect to see some minor side effects from the ChAdOx1 nCoV-19 vaccine such as a sore arm, headache and fever. Saline does not cause any of these side effects. If participants were to receive only this vaccine or a saline control, and went on to develop side effects, they would be aware that they had received the new vaccine. It is critical for this study that participants remain blinded to whether or not they have received the vaccine, as, if they knew, this could affect their health behaviour in the community following vaccination, and may lead to a bias in the results of the study.

2. If Phase 1 goes well, Phase 2 will then extend the maximum age of trial participants to 55-70 years, then over 70.
3. Finally, Phase 3 will see 5,000 volunteers aged over 18 years tested, with half receiving the COVID-19 vaccine.

The researchers explained: “Clear efficacy endpoints will be used to assess the effectiveness of the vaccine, and volunteers from phase I and II will be included in the follow-up.”

How long will the trial last?

The researchers say they’re remaining cautious when mapping out a timeline for the trial, however, scientists working on the vaccine have said they could know within six weeks, from the onset of the clinical trial whether it will work.

They explained: “The best-case scenario is that by the autumn of 2020 we could have an efficacy result from the phase III trial to show that the vaccine protects against the virus, alongside the ability to manufacture large amounts of the vaccine, but these best-case timeframes are highly ambitious and subject to change.”

When will the vaccine be available to the public?

The researchers have purposefully remained tight-lipped about their predicted timelines for a public rollout of the vaccine.

Prof John Bell, a researcher working on the project, explained in a recent (30th April) statement to CNN that the first results should be available in mid- June. Several hundred people have been vaccinated to date. “If we can see evidence of a strong immune response by the middle or the end of May, then I think the game is on,” he said, adding that the next step would then be “the massive issue of how you manufacture at scale many billions of doses.” To this end the Oxford University team is partnering with the pharmaceutical company AstraZeneca, with the aim of manufacturing the vaccine on a large scale.

Are there any other vaccine trials going on?

The Oxford trial is the first in the UK, but several other human vaccine trials are now underway in the US.

Moderna and Inovio have started their trials, and several other research groups have expressed interest in rolling out trials in the coming weeks.

Human trials began on 23rd April 2020.

21. Predictive Oncology

Predictive Oncology has launched an AI Platform for the discovery and development of vaccines against coronavirus. The company has signed an agreement with InventaBioTech to acquire Soluble Therapeutics, which provides it with access to the HSCTM Technology.

Predictive will use the HSCTM Technology along with its predictive modeling platform to deploy an AI discovery platform that can screen the ideal combination of additives and excipients for protein formulations.

22. Sanofi

Vaccine based on Sanofi's recombinant DNA platform, designed to produce an exact genetic match to proteins found on the surface of the virus (the S protein). Sanofi said the DNA sequence encoding the antigen will be combined into the DNA of the baculovirus expression platform and used for rapidly producing large quantities of the coronavirus antigen, which will be formulated to stimulate the immune system to protect against the virus.

In pre-clinical studies, the SARS vaccine candidate was immunogenic and afforded partial protection as assessed in animal challenge models, Phase 1 human studies are between March 2021 and August 2021.

Sanofi expects to produce 600 million doses next year if its clinical trials with GlaxoSmithKline (GSK) goes as planned.

23. Serum Institute of India

Serum Institute of India (SII) is collaborating with Codagenix, a US-based biopharmaceutical company, to develop a cure for coronavirus using a vaccine strain similar to the original virus. The vaccine is currently in the pre-clinical testing phase, while human trials are expected to commence in the next six months. SII is expected to launch the vaccine in the market by early 2022.

24. Tonix Pharmaceuticals Holding

TNX-1800 is a live modified horsepox virus vaccine for percutaneous administration

Tonix said February 26 it has partnered with Southern Research to develop TNX-1800 as a vaccine treatment for COVID-19. TNX-1800 is under development as a potential smallpox preventing vaccine for the U.S. strategic national stockpile and as a monkeypox preventing vaccine.

Tonix Pharmaceuticals Holding Corp and the University of Alberta, a leading Canadian research university, have announced a new research collaboration and exclusive licensing agreement for three new vaccines for the prevention of COVID-19, the novel coronavirus disease identified in 2019 which is caused by SARS-CoV-2 virus

TNX-801 and TNX-1800 are in the pre-IND stage and have not been approved for any indication.

25. Vaxart

Vaccine based on proprietary VAAST™ Platform, Vaxart is developing an oral recombinant vaccine administered in tablet form

Vaxart said January 31 that it plans to generate vaccine candidates based on the published genome of the 2019 COVID-19 (SARS-nCoV-2) and evaluate them in preclinical models based on their ability to generate both mucosal and systemic immune responses. It has five vaccine candidates for preclinical testing

The company plans to start a Phase 1 clinical trial in the U.S. in the second half of 2020,

26. Zydus Cadila

Zydus Cadila announced the launch of an accelerated research programme to develop a vaccine for COVID-19 using two novel approaches. The first approach includes the development of a DNA vaccine against the viral membrane protein of the virus, while a live attenuated recombinant measles virus (rMV) vectored vaccine will be developed in the second approach. The rMV-based vaccine works by inducing specific neutralising antibodies, which will provide protection from the coronavirus infection.

THERAPEUTIC DRUGS

Therapeutic strategies for critically ill patients with COVID-19

- ✓ Antiviral therapy
 - Favipiravir and ribavirin
 - Lopinavir/ritonavir
 - Remdesivir
 - Arbidol
 - Chloroquine and hydroxychloroquine

- ✓ Antibacterial therapy

- ✓ Adjunctive interventions
 - Corticosteroids
 - Thymosin alpha-1
 - Cyclosporine A
 - Interferons
 - Gammaglobulin
 - Tocilizumab

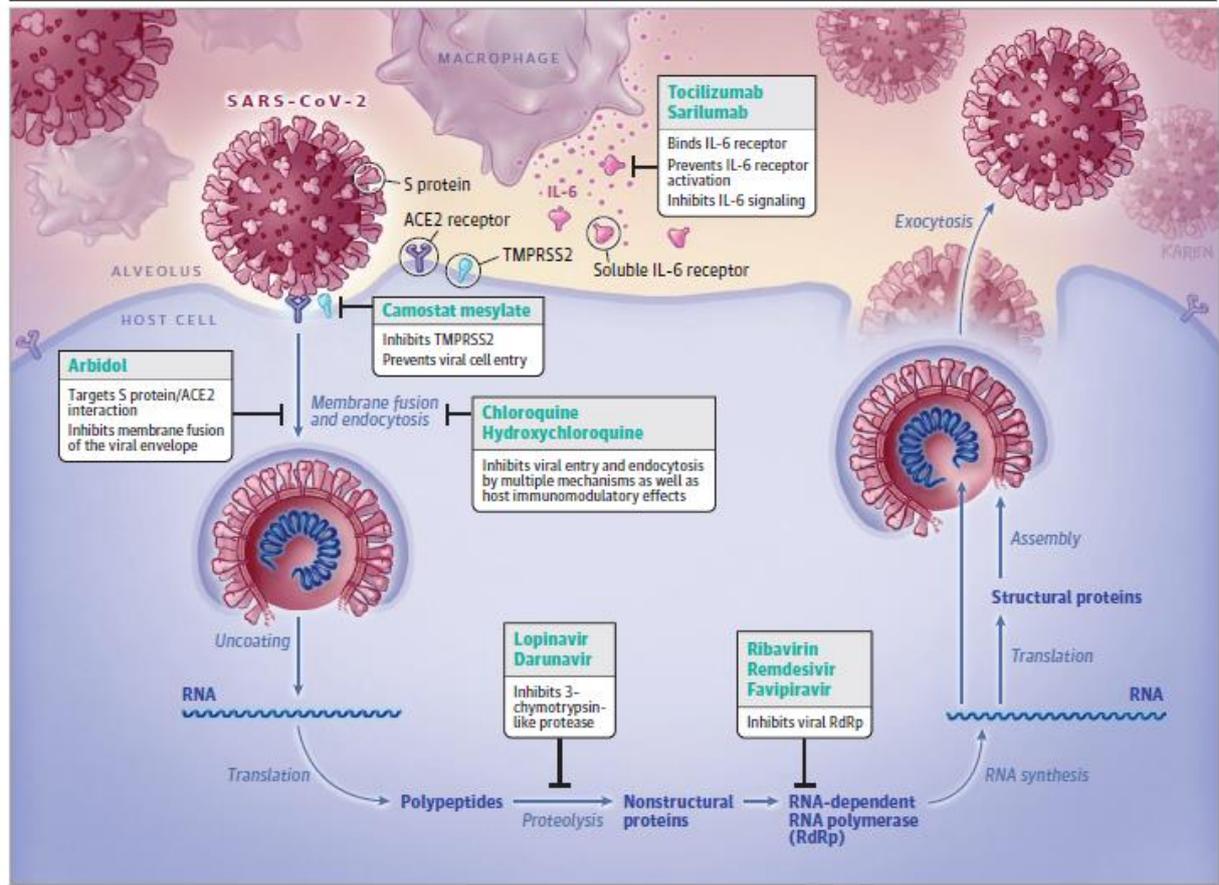
- ✓ Chinese traditional medicine

- ✓ Convalescent plasma

- ✓ Respiratory supportive strategies

VACCINATIONS & THERAPEUTIC DRUGS

Figure. Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Potential Drug Targets



Schematic represents virus-induced host immune system response and viral processing within target cells. Proposed targets of select repurposed and investigational products are noted. ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease.

Assessment of Evidence for COVID-19-Related Treatments: Updated 4/24/2020

The information contained in this evidence table is emerging and rapidly evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner due to the uniqueness of each medical facility's approach to the care of patients with COVID-19 and the needs of individual patients. ASHP provides this evidence table to help practitioners better understand current approaches related to treatment and care. ASHP has made reasonable efforts to ensure the accuracy and appropriateness of the information presented. However, any reader of this information is advised ASHP is not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in the evidence table in any and all practice settings. Any reader of this document is cautioned that ASHP makes no representation, guarantee, or warranty, express or implied, as to the accuracy and appropriateness of the information contained in this evidence table and will bear no responsibility or liability for the results or consequences of its use. Public access to AHFS Drug Information® (<https://www.ahfscdi.com/login>) is available for the next 60 days with the username "ahfs@ashp.org" and password "covid-19." ASHP's patient medication information is available at <http://www.safemedication.com/>.

Select entries were updated on 4/24/2020; these can be identified by the date that appears in the Drug(s) column.

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Table 1. Summary of Pharmacology for Select Proposed COVID-19 Treatments

Agent	Target	Adult dose/administration	Contraindications	Toxicities	Major drug-drug interactions	Special populations
Repurposed agents						
Chloroquine phosphate (Aralen/generic) ⁹⁻¹⁴	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Additional immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells	500 mg by mouth every 12-24 h × 5-10 d. Available as: 250-mg tablets (salt); 500-mg tablets (salt); 500-mg tablets of chloroquine phosphate (salt) = 300-mg chloroquine base. Dose adjustments: Kidney: creatinine clearance <10 mL/min administer 50% of dose. Hepatic: No dose adjustments in hepatic impairment recommended; use with caution. Administration: Preferable to avoid crushing. If needed, may be crushed and mixed with jam, pasteurized yogurt or similar foods	Hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of formulation. Presence of retinal or visual field changes of any etiology (unless benefit outweighs risk)	Common: Abdominal cramps, anorexia, diarrhea, nausea, vomiting. Major: Cardiovascular effects (including QTc prolongation), hematologic effects (including hemolysis with G6PD deficiency, use if benefit outweighs risks), hypoglycemia, retinal toxicity, neuropsychiatric and central nervous system effects, idiosyncratic adverse drug reactions	CYP2D6 and CYP3A4 substrate	May be used in pregnancy if benefit outweighs risks
Hydroxychloroquine sulfate (Plaquenil/generic) ^{9-11,15-20}	Hydroxychloroquine shares the same mechanism of action as chloroquine	400 mg by mouth every 12 h × 1 d, then 200 mg by mouth every 12 h × 4 d; alternative dosing: 400 mg by mouth daily × 5 d or 200 mg by mouth 3 times/d for 10 d. Available as: 200-mg tablets of hydroxychloroquine sulfate (salt) = 155 mg hydroxychloroquine base. Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution. Administration: Manufacturer does not recommend crushing tablets; however, some sources suggest that tablets can be crushed and dispersed with water OR compounded into an oral solution	Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative, or any component of the formulation	Adverse drug reactions similar to chloroquine but less common	CYP2D6, CYP3A4, CYP3A5, and CYP2C8 substrate	May be used in pregnancy if benefit outweighs risks
Lopinavir/ritonavir (Kaletra) ²¹⁻²⁶	3CL protease	400 mg/100 mg by mouth every 12 h for up to 14 d. Available as: lopinavir/ritonavir, 200-mg/50-mg tablets; lopinavir/ritonavir, 100-/50-mg tablets; lopinavir/ritonavir 400-mg/100-mg per 5-mL oral solution (can be given via feeding tubes compatible with ethanol and propylene glycol, contains 42% alcohol). Dose adjustments: No kidney or hepatic dose adjustments recommended; use with caution in hepatic impairment. Administration: Food restrictions: Tablets, take without regard to meals; oral solution, take with food. Do not crush tablets; oral solution not recommended with polyurethane feeding tubes	Hypersensitivity to lopinavir/ritonavir or any of its ingredients, including ritonavir. Co-administration with drugs highly dependent on CYP4503A. Co-administration with potent CYP450 3A inducers	Common: gastrointestinal intolerance, nausea, vomiting, diarrhea. Major: Pancreatitis, hepatotoxicity, cardiac conduction abnormalities	CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 inducer. P-gp substrate; UGT 1A1 inducer	May be used in pregnancy; avoid oral solution if possible due to ethanol content
Umifenovir (Arbidol) ²⁷⁻²⁹	S protein/ACE2, membrane fusion inhibitor	200 mg every 8 h by mouth 7-14 d. Available as (not in the US): 50-mg and 100-mg tablets, capsules and granules. Dose adjustments: Kidney: no dose adjustment necessary. Hepatic: No specific recommendations available, caution in those with hepatic impairment. Administration: Bioavailability 40%	Known hypersensitivity to umifenovir	Allergic reaction, gastrointestinal upset, elevated transaminases	Metabolized by CYP3A4, monitor with strong inducers/inhibitors	Contraindicated in children <2 y of age (increased sensitivity)
Investigational agents						
Remdesivir ³⁰⁻³²	RNA polymerase inhibitor	200 mg × 1, 100 mg every 24 h IV infusion. Available as: 5-mg/mL vial (reconstituted). Dose adjustments: Kidney: Not recommended for GFR <30. No kidney/hepatic dose adjustment currently recommended but holding doses may be considered if significant toxicities occur. Administration: 30-min IV infusion	Exclusion criteria based on specific protocols	Elevated transaminases (reversible), kidney injury	Not a significant inducer/inhibitor of CYP enzymes, monitor with strong inducers/inhibitors	Safety in pregnancy unknown, currently recommended to avoid

(continued)

Table 1. Summary of Pharmacology for Select Proposed COVID-19 Treatments (continued)

Agent	Target	Adult dose/adm in istration	Contraindications	Toxicities	Major drug-drug interactions	Special populations
Favipiravir ^{33,34}	RNA polymerase inhibitor	Doses vary based on indication, limited data available. Available as (not in the US): 200-mg tablet. Dose adjustments: Kidney: no dose adjustment recommended, limited data available, Hepatic: Dose adjustment considered in Child-Pugh C, in creased exposures observed in Child-Pugh class A to C. Administration: Tablet can be crushed or mixed with liquid, bioavailability >95%	Exclusion criteria based on specific protocols	Hyperuricemia, diarrhea, elevated transaminases, reduction in neutrophil count	CYP2C8 and aldehyde oxidase inhibitor, metabolized by aldehyde oxidase and xanthine oxidase	Contraindicated during pregnancy, metabolite found in breast milk
Adjunctive therapies						
Tocilizumab (Actemra) ^{35,36}	IL-6 inhibition - reduction in cytokine storm	400 mg IV or 8 mg/kg × 1-2 doses. Second dose 8-12 h after first dose if inadequate response. Available as: IV infusion injection: 80 mg/4 mL (20 mg/mL); 200 mg/10 mL (20 mg/mL); 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to IV infusion. Dose adjustments: Kidney: No dose adjustments recommended in mild or moderate kidney impairment. Not studied in patients with severe impairment. Hepatic: No dose adjustments recommended (not studied); initiate based on benefit. Administration: Infuse over 60 min, should not be infused concomitantly in the same IV line with other drugs	Known hypersensitivity to tocilizumab or any components of the formulation. Caution in patients with neutropenia (<500 cells/μL) or thrombocytopenia (<50 000/μL)	Common: Increase in upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased AST, infusion related reactions. Major: Hematologic effects, infections, hepatotoxicity, gastrointestinal perforations, hypersensitivity reactions	In vitro data suggested that IL-6 reduces mRNA expression for several CYP450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. May decrease levels of substrates	Safety in pregnancy unknown; may cause harm to the fetus

Abbreviations: ACE2, angiotensin-converting enzyme 2; AST, aspartate aminotransferase; 3CL, 3-chymotrypsin-like; COVID-19, coronavirus disease 2019; CYP, cytochrome P450; G6PD, glucose-6-phosphate-dehydrogenase; GFR, glomerular filtration rate; IV, intravenous; P-gp, P-glycoprotein; UGT1A1, UDP-glucuronosyltransferase family 1 member A1.

JAMA Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)

1. AbbVie

Kaletra® (also marketed as Aluvia; lopinavir/ritonavir)

HIV-1 protease inhibitor indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and children 14 days old and older.

China's National Health Commission authorized Kaletra to treat pneumonia caused by SARS-CoV-2, AbbVie announced on January 27. AbbVie has donated RMB 10 million (\$1.4 million) of Kaletra to Chinese authorities "as an experimental option to support this growing public health crisis."

This is one of the four drugs/drug combinations which is under review by the World Health Organisation (WHO). It was shown to be effective against severe acute respiratory syndrome (SARS) in vitro, and in some clinical trials. Like umifenovir, lopinavir/ritonavir is included in the latest Chinese guidelines using a 200 mg/50 mg capsule at a dose of 2 capsules twice a day for up to 10 days. The medication is being studied alone and in combination with other agents including ribavirin and interferon.

In a completed trial, on 199 patients with severe SARS-CoV-2 infection in Wuhan, China, showed no benefit beyond standard care. Whether earlier intervention is more beneficial should be subject of further studies [Cao B, et al *NEJM* March 18, doi: 10.1056/NEJMoa2001282.]

The combination from published information has been more currently included in French, Belgium, German, US, Singapore and Japanese Guidelines, and is in phase 3 clinical trials. Also the combination with the addition of Interferon beta 1a is now part of the Solidarity clinical trial [Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. *Antiviral Res.* 2020;178:104791. doi:10.1016/j.antiviral.2020.104791]

According to the Oxford COVID-19 Evidence Service Team, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, there is currently no strong evidence for the efficacy of lopinavir/ritonavir in the treatment of COVID-19 (April 14th), primary outcomes of time to clinical improvement and negative pharyngeal SARS-CoV-2 PCR test.

2. AIM ImmunoTech

Ampligen® (rintatolimod). Immune modulator initially developed to treat severe chronic fatigue syndrome, it is a TLR-3 agonist that is being tested as a potential treatment for COVID-19 by the National Institute of Infectious Diseases (NIID) in Japan and the University of Tokyo. It is a broad-spectrum antiviral agent., which has shown 100% protective efficacy against SARS-CoV-1 in animal models.

For the COVID-19 disease early trials started in March in Japan and results have yet to be announced

3. Airway Therapeutics

AT-100, is a recombinant protein which has shown efficacy in preclinical studies in reducing inflammation and infection in the lungs, while also generating an immune response against various respiratory diseases. Airway in March, filed an application with the Respiratory Diseases Branch of the National Institutes of Health (NIH), National Institute of Allergy and Infectious Diseases (NIAID), to evaluate AT-100 (rhSP-D) as a therapeutic for the novel coronavirus (COVID-19). Clinical trials expected soon.

4. Algernon Pharmaceuticals

NP-120 (Ifenprodil)

NP-120 can reduce the infiltration of neutrophils and T-cells into the lungs where they can release glutamate and cytokines respectively. It is already approved to reduce lung fibrosis in other conditions. There is approval for a phase 2b/3 clinical trial for patients with advanced COVID-19 lung disease.

5. APEIRON Biologics

APN01

Recombinant human angiotensin-converting enzyme 2 (rhACE2) developed for the treatment of acute lung injury, acute respiratory distress syndrome, and pulmonary arterial hypertension.

Vienna-based APEIRON on February 26 launched a pilot investigator-initiated clinical trial in China designed to assess APN01 as a treatment for patients with severe SARS-CoV-2 infection. The randomized, unblinded trial will treat 24 patients for seven days to obtain preliminary data on the impact of rhACE2 on biological, physiologic, and clinical outcomes, as well as safety. Suzhou-based Angalharma is coordinating the Chinese clinical trial, with support from dMed Pharmaceutical, a CRO based in Shanghai.

In addition, the company has secured approvals from regulatory agencies in Austria, Germany and Denmark to conduct a Phase II clinical trial of APN01 for the treatment of Covid-19.

6. Asclepis Pharma

Ganovo® danoprevir plus ritonavir; ASC09 and ritonavir; ASC09 and oseltamivir; ritonavir and oseltamivir;

HIV protease inhibitors.

A clinical study has been published on 11 patients taking danovepir plus ritonavir: The data from this small-sample clinical study showed that danoprevir boosted by ritonavir is safe and well tolerated in all patients, of whom 8 patients showed significant clinical manifestations such as fever, and dry coughing, while 3 patients didn't show significant clinical manifestation. After 4 to 12-day treatment all eleven patients enrolled, were discharged well with significantly reduced viral load [*Chen H et al. doi: <https://doi.org/10.1101/2020.03.22.20034041>*].

On February 2, Asclepis said it is actively assisting “relevant medical institutions and medical researchers” in clinical trials assessing the combination of Asclepis’ ASC09 and ritonavir for COVID-19, following a request they made to the company. Phase 3 trials are now ongoing in several sites in China.

7. Bayer and numerous Chinese manufacturers

Chloroquine phosphate (marketed by Bayer as Resochin®)

Phosphate salt of chloroquine, a quinoline compound with antimalarial and anti-inflammatory properties. Resochin was discovered by Bayer and introduced into clinical

practice in 1947 to treat malaria. It is also used in the clinical management of autoimmune diseases including erythematosus lupus and rheumatoid arthritis.

Evaluated in clinical trials in over 10 hospitals in Beijing, as well as in south China's Guangdong Province and central China's Hunan Province, where it has "shown fairly good efficacy" according to Sun Yanrong, deputy head of the China National Center for Biotechnology Development under the Ministry of Science and Technology (MOST), the state-owned Xinhua news agency reported on February 17. Chloroquine and remdesivir (developed by Gilead) were "highly effective in the control of 2019-nCoV infection in vitro," a team of Chinese researchers reported in a study published February 4 in *Cell Research*. After China's National Health Commission included chloroquine phosphate in its latest treatment guidelines for COVID-19 pneumonia, eight Chinese companies sped up manufacturing and supply of the drug, *Shanghai Daily* reported February 20. Some clinical studies have also been undertaken in France, mostly in combination with Azithromycin (antibiotic). Most of the studies have not been used in severe cases, and in the USA there is an ongoing study to use high doses (results are anticipated shortly – NCT, 04308668, 2020).

Since adverse effects are quite limited and effectiveness satisfactory, future studies perhaps should also focus on severe cases to expand the knowledge on its effectiveness.

A large ongoing study is comparing hydroxychloroquine's clinical outcomes to carrimycin, lopinavir/ritonavir, and umifenovir, but the study is not anticipated to conclude before February 2021. The most recent Chinese guidelines on COVID-19 recommend chloroquine phosphate 500 mg twice a day for up to 10 days.

Chloroquine phosphate or hydroxychloroquine sulfate (plaquenil) is used alone or in combination with antibiotic in France, Belgium, Germany, Canada, USA, Singapore and Japan.

8. Beijing Staidson Biopharma and InflaRx

IFX-1 - Anti-C5a monoclonal antibody in development for COVID-19 as well as hidradenitis suppurativa

The Chinese authorities approved clinical trials of IFX-1 as a COVID-19 treatment in February. This is already in phase 2 clinical trials for vasculitis

9. BenevolentAI

Baricitinib

This already approved drug for COVID-19 was identified by Benevolent AI using artificial intelligence. This substance is believed to reduce the ability of the corona virus to enter the alveolar epithelial cells, probably by blocking the ACE2 pathway.

Baricitinib enters a randomised-controlled trial with the US National Institute of Allergy and Infectious Diseases (NIAID); predicted to inhibit COVID-19 infection of human lungs and reduce inflammatory damage.

Baricitinib is an already approved drug developed by Eli Lilly and Incyte for the treatment of rheumatoid arthritis and is being studied for other indications. The randomised trial announced by Eli Lilly today with the US National Institute for Allergies and Infectious Diseases (NIAID) will investigate the efficacy and safety of baricitinib as a potential treatment for patients with serious COVID-19 infections. The study will begin in the US in late April with planned expansion to additional sites in Europe and Asia. Results are expected within the next two months.

10. BeyondSpring

BPI-002

It has the ability to activate CD4+helper T cells and CD8+ cytotoxic T cells, generating an immune response

11. Biocryst

Galidesivir (BCX4430)

Nucleoside RNA polymerase inhibitor designed to disrupt the viral replication process

Shown broad-spectrum activity in vitro against more than 20 RNA viruses in coronaviruses, by blocking the synthesis of RNA.

The drug has already shown survival benefits in patients against deadly viruses such as Ebola, Zika, Marburg, and Yellow fever.

Galidesivir is currently in advanced development stage under the Animal Rule to combat multiple potential viral threats including coronaviruses, flaviviruses, filoviruses, paramyxoviruses, togaviruses, bunyaviruses, and arenaviruses. For the SARS-CoV-2 virus a clinical trial is initiated in Brazil with 24 patients initially, to be expanded later according to the initial results. The trial is supported by the NIH (US)

12. BioXyTran

BXT-25 - to treat late-stage acute respiratory distress syndrome (ARDS)

Anti-necrosis drug whose glyco-polymer structure consists of hybrid molecules integrating the Hemoglobin molecule and a proprietary polymer chemical structure. BXT-25 is company's lead product candidate, designed to carry oxygen to tissues when the flow of blood is blocked.

Boston-based Bioxytran said February 5 that it is exploring partnering with "international drug companies" to develop BXT-25 as a treatment for Acute Respiratory Distress Syndrome (ARDS) in end-stage patients with SARS-CoV-2.

The diffusion of oxygen to the blood is compromised in patients suffering from ARDS leading to fluid build-up in the lungs. Since BXT-25 is 5,000 times smaller than red blood cells, the drug can help in supplying oxygen to the vital organs and enable the patient to recover and survive.

The company will use MDX Life Sciences' MDX Viewer to assess the safety and efficacy of the drug.

13. CEL-SCI

CEL-SCI is developing immunotherapy against COVID-19 using its proprietary LEAPS peptide technology, which utilises conserved areas of the coronavirus proteins to generate T-cell responses and reduce viral load. The technology can also be used to develop immunotherapeutic peptides with both antiviral and anti-inflammatory properties.

The peptides developed using this technology can help in reducing tissue damage from inflammation caused due to lung infection, which is a major cause of mortality in elderly patients.

14. Celularity and Sorrento Therapeutics

CYNK-001 - Allogeneic, off-the-shelf, placental-derived Natural Killer (NK) cell therapy

The companies on January 30 launched a clinical and manufacturing collaboration designed to expand the therapeutic use of Celularity's CYNK-001 to COVID-19. Sorrento and Celularity agreed to assess CYNK-001 as a potential novel therapy for coronaviruses, specifically SARS-CoV-2. Sorrento—which owns 25% of Celularity—agreed to use current existing capacity in its cGMP cell therapy manufacturing facilities in San Diego to supplement Celularity's new cGMP facility in Florham Park, NJ. Sorrento said it is already in contact with “leading” scientists and local Chinese experts to discuss clinical validation and logistics requirements for fast-tracking CYNK-001 in China.

15. Chugai Pharmaceutical and Zhejiang Hisun Pharmaceutical

Tocilizumab (Actemra)

Humanized mAb targeting interleukin-6

A 94-patient trial assessing Tocilizumab has been registered with Chinese authorities by The First Affiliated Hospital of University of science and technology of China (Anhui Provincial Hospital) (ChiCTR2000029765). A phase 2 trial in Italy (this is planned to include 330 patients hospitalised with first signs of respiratory failure. In addition a randomised phase 3 clinical trial has been approved by FDA (enrolment is expected to start in April 2020).

16. Columbia University

Researchers at Columbia University have been awarded a \$2.1m grant by the Jack Ma Foundation to develop a cure for coronavirus. Four different teams at the university will adopt various approaches towards the development of a vaccine against coronavirus.

17. CytoDyn

Leronlimab (PRO 140) - Humanized IgG4 monoclonal antibody. Leronlimab is CytoDyn's lead candidate, and is a CCR5 antagonist with potential for multiple therapeutic indications.

CytoDyn has initiated a phase 2b/3 randomised clinical trial in the US, targeting 390 COVID-19 patients. It is being proposed as a treatment for mild-to-moderate respiratory complications that occur in patients with the disease as well as severely and critically ill patients.

The randomized, double-blind, placebo-controlled study will test the efficacy and safety of leronlimab initially in 75 patients.

18. Emergent BioSolutions

Emergent BioSolutions is developing two plasma-derived product candidates or hyperimmunes using its hyperimmune platforms for the treatment of coronavirus. The hyperimmune platforms have been used previously for the development of several approved products including vaccines for smallpox, botulism, and anthrax.

The hyperimmunes are polyclonal antibodies derived from plasma, which are capable of generating an immune response and protecting against infection. Product candidate derived from human plasma is named COVID-HIG, while COVID-EIG is derived from equine plasma. Both will be explored for the treatment of patients with a severe case of infection.

19. Enanta Pharmaceuticals

Enanta Pharmaceuticals has announced its plans to develop antiviral drug candidates to treat COVID-19 patients. The company is testing compounds from its existing antiviral compound library for potential efficacy in treating COVID-19. It has also launched a drug discovery programme to develop direct-acting drug candidates to treat COVID-19.

20. Fujifilm Holdings and Zhejiang Hisun Pharmaceutical

Favipiravir (marketed by Fujifilm as Avigan and by Hisun in China as Favilavir)

Broad spectrum anti-viral agent that is designed to selectively and potently inhibit the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Japan has approved Avigan for novel or re-emergent influenza and was previously used to treat Ebola patients in Guinea.

Apart from trials in Japan, This promising anti-viral is currently being tried in several countries, in phase 3 trials.

Cyprus is also participating in this trial with 20 patients. Study shown that use of 1600mg twice the first day and 600mg twice daily until the 14th day, gave positive results in combating COVID-19 as compared to LPV/RTV.

The Russian Direct Investment Fund (RDIF) with a local drug maker will start the production of a new drug designed analogue of the favipiravir drug initially developed by Fujifilm Holdings approved for the treatment of influenza in Japan in 2015 and showed effectiveness in patients with coronavirus and Shenzhen.

The trade name is AVIGAN and the plan is to produce 600.000 packages this year.

21. Gilead Sciences

Remdesivir (GS-5734). Originally under development for Ebola, remdesivir incorporates into nascent viral RNA chains, and causes premature termination.

Several phase 3 clinical trials are ongoing at present. The only known results are from the university of Chicago, where 125 cases have been recruited for phase 3 trial and have responded well to IV remdesivir [<https://www.jagranjosh.com/general-knowledge/what-is-remdesivir-and-can-it-be-useful-in-treating-covid19-1586947150-1>]. It has been shown that the drug can reduce recovery time by about 30%. Based on these initial favourable results the WHO has included this anti-viral agents in its Innovator trial and the US FDA has approved it for emergency use in this pandemic, based on a study involving 1063 patients. There have been some negative results from a trial in China but this was regraded a small case experience.

Gilead's notable clinical trials:

1. The National Institute of Allergy and Infectious Diseases trial has enrolled patients in a randomized, double-blind, placebo-controlled Phase 3 trial evaluating 1,063 hospitalized patients with COVID-19 at 68 sites worldwide, including at three sites in Singapore and South Korea, according to the NIAID. However, the majority of the study locations are in the U.S. The study began Feb. 21 and is expected to conclude April 1, 2023.

2. A Gilead-sponsored randomized, open-label Phase 3 trial is testing remdesivir in 1,600 patients with moderate COVID-19. It previously said it would enroll 600 participants. The trial started enrolling patients in March, with results to come in May. The clinical trial listing states the study is taking place in 13 countries, including Hong Kong, Singapore, South Korea and the U.S.

3. A Gilead-sponsored randomized, open-label Phase 3 trial is evaluating remdesivir in 6,000 patients with severe COVID-19. The trial started enrolling patients in March, and early results based on 397 patients included in the initial phase of the study were used to inform the EUA. The clinical trial listing states the study is taking place in Hong Kong, Singapore, South Korea and the U.S.

Results: It was reported on April 16 that University of Chicago Medicine researchers saw "rapid recoveries" in 125 COVID-19 patients remdesivir, though that data isn't part of the full clinical trial data set.

What's next: Gilead plans to donate 1.5 million vials, about 140,000 10-day courses of treatment, of the drug through June. It also said on May 5, that it plans to contract with pharmaceutical manufacturers abroad to ensure access to remdesivir outside of the U.S.

At this time, evaluation of an oral version of remdesivir has not been proposed and it is unknown if this antiviral would be useful for patients whose symptoms are not severe enough to warrant hospitalization.

22. Incyte, Shanghai Hengrui Pharmaceutical

Camrelizumab and thymosin

Humanized monoclonal antibody targeting PD-1 (Camrelizumab); 5-Da polypeptide hormone secreted by the thymus gland (thymosin)

Chinese clinical trials assessing the combination treatment have been registered by Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital) (ChiCTR2000029806) and Southeast University (NCT04268537). At present (May 2020) no updated data have been made available

23. Innovation Pharmaceuticals

Brilacidin -Defensin mimetic in Phase II development in oral mucositis in Head and Neck Cancer patients

Innovation said February 24 that it submitted a Material Transfer Agreement with an unidentified “leading U.S.-based virology laboratory” to study Brilacidin as a potential novel treatment for SARS-CoV-2. If lab tests prove successful, Innovation said, it will expedite research and clinical development of Brilacidin “via pharmaceutical partnerships, academic collaborations and government grants.” Innovation has also submitted a preliminary summary of Brilacidin’s potential for treating coronavirus to the Biomedical Advanced Research and Development Authority (BARDA). As of May 8th, this drug is still not yet in human trials for COVID-19

24. Janssen Pharmaceutical Cos. (Johnson & Johnson)

Prezcobix™ (darunavir and cobicistat) is an HIV protease inhibitors (Prezcobix)

Janssen has provided DVR-based medicines to support three clinical studies in China. Unpublished results from one clinical study show that five days of darunavir and cobicistat was not effective in treating COVID-19. As further preclinical and / or clinical data become available, thjis information will be updated

A Chinese trial is assessing Precobix or the lopinavir-ritonavir combination combined with thymosin a1 (ChiCTR2000029541).

25. Mateon Therapeutics

Mateon Therapeutics has launched an antiviral response programme to develop coronavirus treatments using its therapeutic and artificial intelligence (AI) platforms. It has also established a division, which will adopt a multi-modal approach to developing COVID-19 treatments as well as other future zoonotic outbreaks.

On April 24th, Mateon published a report in the biomedical journal *Annals of Pulmonary and Critical Care Medicine* regarding the medical-scientific rationale for its planned randomized, placebo-controlled, Phase 2 Study of OT-101 (TGF- β inhibitor) in COVID-19 patients with hypoxemic respiratory failure. [Uckun FM, Trieu V. Medical-Scientific Rationale for a Randomized, Placebo-Controlled, Phase 2 Study of Trabedersen/OT-101 in COVID-19 Patients with Hypoxemic Respiratory Failure. *Annals of Pulmonary and Critical Care Medicine* 2020; 3(1); 01-09, and Hwang L, Cynthia L, Vuong N Trieu. COVID-19 Epidemic: China and ex-China. *Open Acc Biostat Bioinform.* 3(1). OABB.000552. 2020. DOI: 10.31031/OABB.2020.03.000552.]

26. NanoViricides

Antiviral therapy based on company's novel nanomedicines platform.

Broad-spectrum virus-binding ligand: "It is like a 'Venus-Fly-Trap' for the virus," says Anil R. Diwan, PhD, President and Executive Chairman.

The Company has worked on developing an animal model to test anti-coronavirus effectiveness in vivo using a model coronavirus that binds to the same ACE2 ("angiotensin convertase enzyme 2") receptor as SARS-CoV-2, namely human coronavirus NL-63 (hCoV-NL63). The Company anticipates using this animal model to obtain indications of effectiveness of the nanoviricide test drug candidates against the model coronavirus in vivo.

27. Novartis

Jakavi® (ruxolitinib)

New clinical trial to evaluate Jakavi® (ruxolitinib) a well-established JAK inhibitor) in patients with COVID-19 associated cytokine storm (severe immune overreaction (to date licensed for myelofribosis and polycythemia vera).

A global phase III clinical trial evaluating ruxolitinib (Jakafi) in combination with standard of care for the treatment of cytokine storm associated with coronavirus disease 2019 (COVID-19) in patients 12 years and older has been initiated, was announced by Incyte on April 21st. This is the first randomized, placebo-controlled phase III study to evaluate the efficacy and safety of this indication.

28. OyaGen

OYA1 has been found effective in inhibiting SARS-COV-2 from replicating in cell culture. OYA1 was approved earlier as an investigative drug for cancer but abandoned due to lack of efficacy.

Now, OyaGen has announced positive findings from collaborative research of a drug candidate, OYA1, for Covid-19 treatment. The research was conducted in partnership with the National Institute of Allergy and Infectious Diseases' Integrated Research Facility.

Cell culture infectivity studies demonstrated strong dose-dependent antiviral activity of OYA1, compared to chlorpromazine HCl, against live SARS-CoV-2, the novel coronavirus that causes Covid-19. OYA1 is said to possess broad-spectrum antiviral activity in lab assays against coronaviruses SARS-CoV-2 and MERS-CoV. It also has antiviral activity against filoviruses such as Ebola virus. However, the drug has not yet reached clinical trial stage.

29. Pfizer

Pfizer announced that it has identified certain under development antiviral compounds that may be effective in treating coronavirus. The company is planning to partner with a third party to screen and identify potential compounds by the end of March and begin testing in April.

30. Pharmstandard

Arbidol (umifenovir), a membrane fusion inhibitor developed as a treatment for influenza

Pharmstandard is assessing Arbidol in clinical trials as monotherapy and in combinations that include AbbVie's Kaletra (See above), Ascleptis Pharma's ASC09 (See above), lopinavir, ritonavir, carrimycin, and Bromhexine Hydrochloride (enrolling by invitation). Five trials including Arbidol were listed on ClinicalTrials.gov. China's Ruijin Hospital is

conducting the monotherapy trial (NCT04260594), while various Chinese hospitals are investigating the combination therapies (NCT04252885, NCT04273763, NCT04261907, NCT04286503).

Umifenovir (Arbidol) monotherapy offers little benefit, according to a study published online April 17 in Med.

31. Regeneron Pharmaceuticals

REGN3048 and REGN 3051

Discovered by Regeneron, the combination of neutralising monoclonal antibodies REGN3048 and REGN3051 leveraging Regeneron's monoclonal antibody discovery platform called VelocImmune® (part of the company's VelociSuite™ technologies).

It is being studied against coronavirus infection in a first-in-human clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), which will be initiated in June. The safety and tolerability of the drug will be studied in 48 patients.

Both the antibodies bind to S-protein of MERS coronavirus. The intravenous administration of the drug in the mouse model of MERS resulted in the high-level neutralisation of the MERS coronavirus in circulating blood with reduced viral loads in the lungs.

On February 4, The Biomedical Advanced Research and Development Authority (BARDA) said it was expanding upon an earlier partnership agreement with Regeneron to develop "multiple monoclonal antibodies that, individually or in combination, could be used to treat new treatments."

32. Regeneron Pharmaceuticals & Sanofi

Kevzara® (sarilumab)

Regeneron has partnered with Sanofi to evaluate Kevzara®, a fully-human monoclonal antibody, in a phase two/three clinical trial in patients with severe COVID-19 infection, which started in March. Kevzara® is approved for the treatment of rheumatoid arthritis and is known to block the interleukin-6 (IL-6) pathway, which causes an overactive inflammatory response in the lungs of COVID-19 patients.

It will test 400 patients in about 16 US sites. The aim is to evaluate if the drug lessens patient fevers and their need for supplemental oxygen. The Phase 3 trial will evaluate if Kevzara prevents deaths and reduces need for mechanical ventilation, supplemental oxygen, or hospitalization.

The next phase of the study will also only include a higher dose of the drug (400 milligrams) and the placebo, and not the lower dose of 200 milligrams used in the mid-stage trial.

33. Roche

Actemra

Actemra by Roche to treat coronavirus-related complications. China approved the use of Roche's Actemra for the treatment of severe complications related to coronavirus. Drugs like Actemra have the ability to prevent cytokine storms or overreaction of the immune system, which is considered as the main reason behind organ failure leading to death in some coronavirus patients.

In a small 21-person trial in China it was found that some patients on Actemra, reported reductions in fever, and 7% of them had a reduced need for supplemental oxygen within days of starting treatment.

Actemra is also being further evaluated in a clinical trial in China, which is expected to enroll 188 coronavirus patients. The clinical trial is expected to be conducted until May 10. In addition, Roche has initiated a Phase 3 clinical trial evaluating Actemra as a treatment for patients with COVID-19 who have been hospitalized with severe pneumonia. Around 330 patients are being enrolled in 55 sites in the U.S. and elsewhere in the world. The company plans to examine patient mortality and need for mechanical ventilation or an intensive care unit stay among other primary and secondary endpoints. Results are expected in early summer.

34. Southwest Research Institute

Southwest Research Institute is using its virtual screening called Rhodium to identify potential drug candidates for treating coronavirus from more than two million drug compounds. The most promising compounds will be identified for further development.

35. Takeda Pharmaceutical Company

Takeda Pharmaceutical Company has announced plans to develop a plasma-derived therapy against coronavirus. The anti-SARS-CoV-2 polyclonal hyperimmune globulin (H-IG) therapy will be designed to treat high-risk patients. The H-IG therapy includes concentrated pathogen-specific antibodies derived from plasma of recovered patients.

These antibodies have the potential to generate an immune response when injected into a new patient, but are still in a preclinical phase.

36. Tiziana Life Sciences

The company developed a monoclonal antibody named TZLS-501 which is a human anti-interleukin-6 receptor (IL-6R). It helps in preventing lung damage and elevated levels of IL-6. This technology enables direct delivery of anti-IL-6 receptor (anti-IL-6R) monoclonal antibodies (mAbs) into the lungs using a handheld inhaler or nebuliser.

The Company has submitted (APRIL 2020) a provisional patent application for the delivery technology. Following this it will be introduced to clinical trials.

37. Vir Biotechnology

Vir Biotechnology, a clinical-stage immunology company, announced on 12 February that it has identified two monoclonal antibodies that can bind to the virus that causes COVID-19. The antibodies target the spike (S) protein of the virus by entering through the cellular receptor ACE2.

Vir has also partnered with Alnylam Pharmaceuticals to identify siRNA candidates targeting SARS-CoV-2. The companies said they aim to file for an investigational new drug application by the end of 2020.

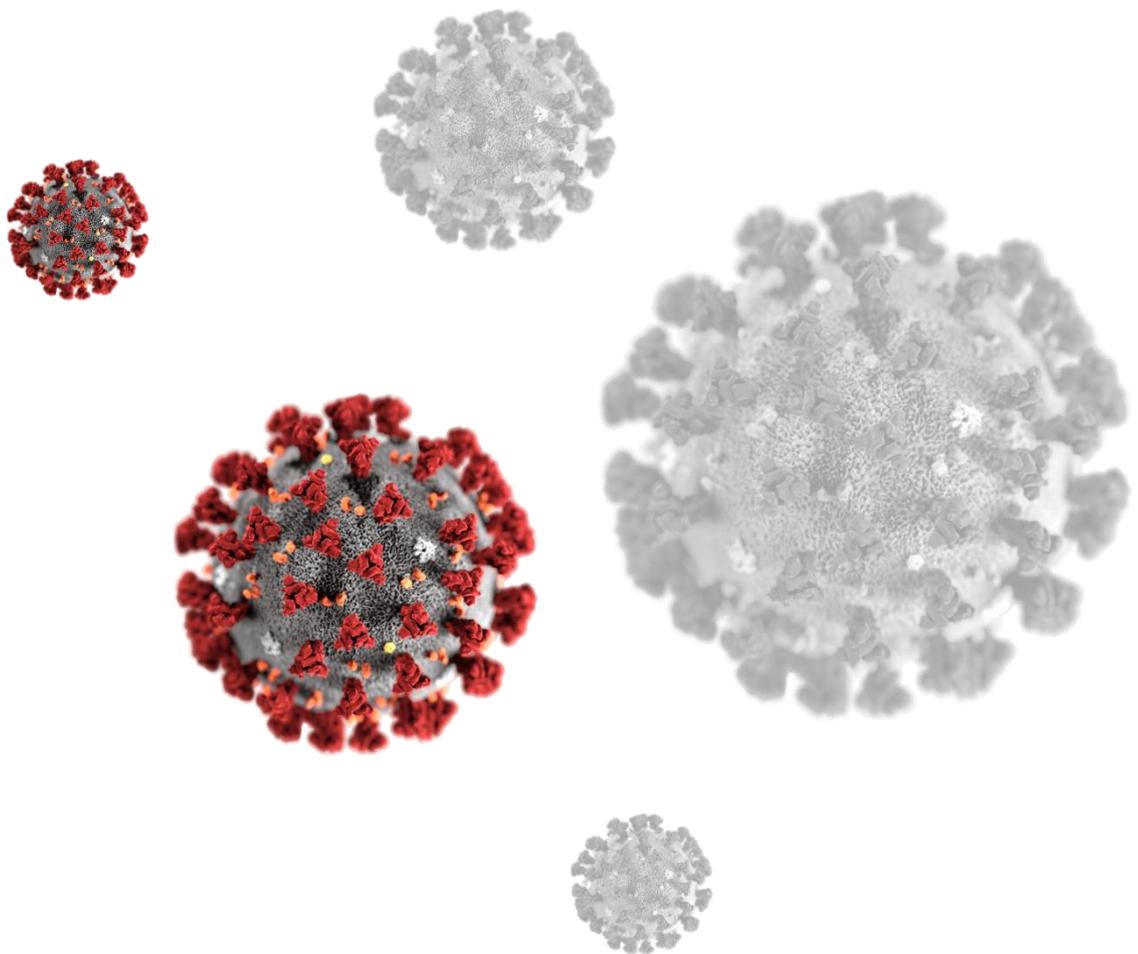
Starting Feb. 25, the company is collaborating with Shanghai-based WuXi Biologics to test monoclonal antibodies as a treatment for COVID-19 in China and elsewhere.

It has formed another partnership with Biogen for cell line and process development and manufacturing of the antibodies.

Plasma derived and immune response therapy – convalescent sera

Post- infection plasma as a source of antibodies to the virus is being investigated at various locations but at present effectiveness has not been tested in infected patients. Such passive immunity may be used to help infected individuals, before vaccinations become available to induce active immunity in the populations. Convalescent plasma is still investigational, in terms of both safety and effectiveness.

Monoclonal antibody drugs may also fall into the category of passive immunity since they target specific proteins of the virus. They are being discussed above under drug therapies



Review of the HIV drugs for coronavirus treatment

Abbvie's HIV protease inhibitor, lopinavir is being studied along with ritonavir for the treatment of MERS and SARS coronaviruses. The repurposed drug is already approved for the treatment of HIV infection under the trade name Kaletra®.

The combination is listed in the WHO list of essential medicines. Lopinavir is believed to act on the intracellular processes of coronavirus replication and demonstrated reduced mortality in the non-human primates (NHP) model of the MERS.

Lopinavir/ritonavir in combination with ribavirin showed reduced fatality rate and milder disease course during an open clinical trial in patients in the 2003 SARS outbreak.

Cipla is also reportedly planning to repurpose its HIV drug LOPIMUNE, which is a combination of protease inhibitors Lopinavir and Ritonavir, for the treatment of coronavirus.

A licensed generic of Kaletra®, LOPIMUNE is currently available in packs of 60 tablets each, containing 200mg of Lopinavir and 50mg of Ritonavir.

Janssen Pharmaceutical Companies, a subsidiary of Johnson & Johnson, donated its PREZCOBIX® HIV medication (darunavir/cobicistat) for use in research activities aimed at finding a treatment for COVID-19.

Darunavir is a protease inhibitor marketed by Janssen. Anecdotal reports suggest darunavir as potentially having antiviral activity against COVID-19. It is, however, currently approved only for use with a boosting agent, and in combination with other antiretrovirals, for the treatment of HIV-1.

Janssen has no in vitro or clinical data to support the use of darunavir as a treatment for COVID-19. The drug is in the process of being evaluated in vitro for any potential activity against the coronavirus.

Further, Janssen has partnered with the Biomedical Advanced Research and Development Authority (BARDA) to expedite the development of a COVID-19 treatment.

News & Updates

European Medicines Agency (EMA)

EMA launched on April 17th an enhanced fast-track monitoring system to help prevent and mitigate supply issues with crucial medicines used for treating COVID-19 patients.

Under this system, each pharmaceutical company is appointing a single contact point (industry single point of contact or i-SPOC) who will report to EMA all ongoing or anticipated shortages of medicines used for treating COVID-19, irrespective of their authorisation route. This mechanism is similar to the single point of contact (SPOC) network that EMA and the national competent authorities already use to exchange information on shortages. Initially, the system will focus on medicines used in intensive care (such as anaesthetics, antibiotics, resuscitation drugs and muscle relaxants), which are in greatest demand, before extending to a broader range of medicines.

In addition, EMA offers medicine developers several opportunities for early dialogue and consultation before submitting a marketing authorisation application. This is intended to provide regulatory and scientific support to facilitate the preparation of applications and enable a smooth validation and assessment procedure.

The World Health Organisation (WHO)

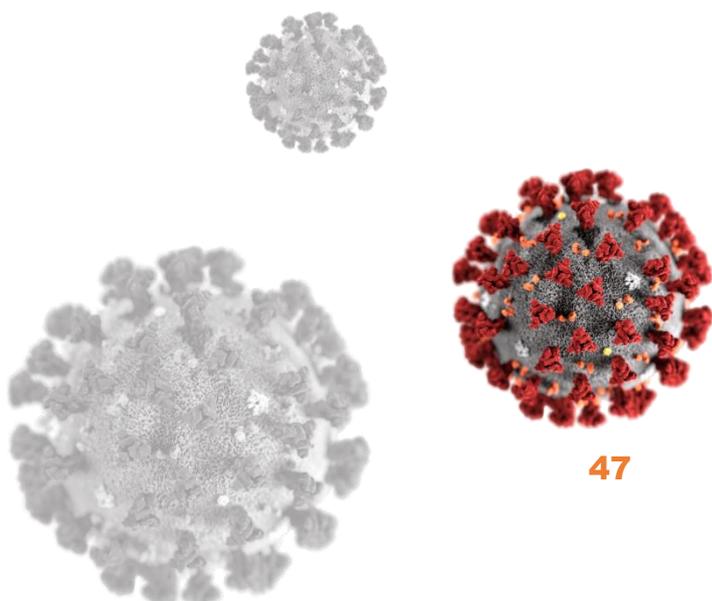
- Four drugs or drug combinations already licensed and used for other illnesses will be tested by WHO and 10 countries have indicated their interest to take part in the trial:
 1. Remdesivir (by Gilead)
 2. Lopinavir and Ritonavir (sold as Kaletra or Aluvia by AbbVie)
 3. Lopinavir and Ritonavir plus Interferon β ; and
 4. the antimalarial drug Chloroquine.
- Like Umifenovir used in China, Lopinavir/ Ritonavir use a 200gm/50mg capsule at a dose of 2 capsules twice a day for up to 10 days. The medication is studied alone or in combination with others including ribavirin and interferon.
- Corticosteroids- Interim guidance from WHO recommends against using them in patient with COVID-19 unless they have another indication.

In the meantime, however, a plethora of other combinations are either under consideration or in studies/trials e.g. (i) interferon alfacon-1 with corticosteroids and (ii) ribavirin with corticosteroids

- FDA allows treatment of life threatening COVID-19 cases using blood from patients who have recovered. It is a temporary authorization under FDA's investigational NEW DRUG APPLICANTS (INDs) exemption.

Convalescent plasma transfusion has been used against H1N1 flu, and SARS and MERS epidemic with varying results. It is not new and is relatively safe.

- May 7th. Convalescent plasma: Trials to treat COVID-19 using the blood plasma from those who have already recovered from the illness have begun. The first 14 units of convalescent plasma from former coronavirus patients have been supplied to three NHS trusts, and transfusions have already taken place.
- Triple combination of Interferon β -1b, lopinavir-ritonavir, and ribavirin, was tested in 127 corona infected patients in Hong Kong, with mild to moderate symptoms. The combination was found superior to in alleviating symptoms and shortening the duration of viral shedding, compared to lopinavir-ritonavir alone. The study was published on the 8th of May edition of the Lancet [[https://doi.org/10.1016/S0140-6736\(20\)31042-4](https://doi.org/10.1016/S0140-6736(20)31042-4)]



CLINICAL MANAGEMENT OF COVID-19 IN SELECTED COUNTRIES

Current therapeutic practices - COVID-19			
Country	Drugs used	Administration	Source
France	remdesivir	people \geq 40 kg : 200 mg/ day, then 100 mg/ day from day 2 to day 10	Haut Conseil de la santé publique, Avis relatif aux recommandations thérapeutiques dans la prise en charge du COVID-19 (complémentaire à l'avis du 5 mars 2020), p. 3 - available at https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=785
	Combination of lopinavir/ritonavir	2 pills of lopinavir/ritonavir 200/50 mg (a total of 400/100 mg) twice/day for 14 days	Haut Conseil de la santé publique, Avis relatif aux recommandations thérapeutiques dans la prise en charge du COVID-19 (complémentaire à l'avis du 5 mars 2020), p. 4 - available at https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=786
	hydroxychloroquin	400 mg twice/day in day 1, then 400 mg once/day for 9 days (Detailed guidance in Table 2, p.8)	Haut Conseil de la santé publique, Avis relatif aux recommandations thérapeutiques dans la prise en charge du COVID-19 (complémentaire à l'avis du 5 mars 2020), p. 6 - available at https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=787
Belgium	hydroxychloroquine sulphate (Plaquenil)	400mg BID on day 1, followed by 200mg BID on days 2-5 (max. 5 days) (Detailed guidance in Table 2, p.8)	Interim Clinical Guidance for Adults with suspected or confirmed COVID-19 in Belgium, p.5 - available at https://epidemiology.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf
	chloroquine	a total of 25 mg/kg within 3 days - restricted to hospitalised patients	Interim Clinical Guidance for Adults with suspected or confirmed COVID-19 in Belgium, p.5 - available at https://epidemiology.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf
	lopinavir/ritonavir	a second choice, when hydroxychloroquine is contraindicated / to be administered early in the course of the disease (within 12 days after symptoms onset)	Interim Clinical Guidance for Adults with suspected or confirmed COVID-19 in Belgium, p.5 - available at https://epidemiology.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf
United Kingdom	No data		
Germany	No	Use of investigational anti-COVID-19 therapeutics (Lopinavir/Ritonavir, Hydroxychloroquin, Favirpiravir, Camostat) should be done under ethically approved, randomized, controlled trials.	Robert Koch-Institut, Notes on the detection, diagnosis and therapy of Patients with COVID-19, p.6 - available at https://www.rki.de/DE/Content/Kommissioner/Stakob/Stellungnahmen/Stellungnahme-Covid-19_Therapie_Diagnose.html
Canada	No	Use of investigational anti-COVID-19 therapeutics should be done under ethically approved, randomized, controlled trials.	Clinical management of patients with moderate to severe COVID-19 - Interim guidance - available at: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html

VACCINATIONS & THERAPEUTIC DRUGS

United States (state level)	hydroxychloroquine	400mg BID x2 doses, then 200mg PO BID for 5-10 days	Nebraska Medicine, COVID-19 Antiviral and Pharmacotherapy Recommendations - available at: https://www.nebraskamed.com/sites/default/files/documents/covid-19/covid19-antiviral-pharmacotherapy-recommendations.pdf
	lopinavir/ritonavir	400/100mg (2 tabs) BID for 5-10 days	Nebraska Medicine, COVID-19 Antiviral and Pharmacotherapy Recommendations - available at: https://www.nebraskamed.com/sites/default/files/documents/covid-19/covid19-antiviral-pharmacotherapy-recommendations.pdf
	remdesivir (compassionate use)	-	Nebraska Medicine, COVID-19 Antiviral and Pharmacotherapy Recommendations - available at: https://www.nebraskamed.com/sites/default/files/documents/covid-19/covid19-antiviral-pharmacotherapy-recommendations.pdf
Singapore	Remdesivir	200 mg IV loading, 100 mg IV daily x 5 to 10 days (as part of clinical trial)	Singapore National Center for Infectious Diseases, Interim Treatment Guidelines for COVID-19 (Version 1.0, dated 2 April 2020) - available at: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx
	Lopinavir/ritonavir	400/100 mg BD x 14 days	Singapore National Center for Infectious Diseases, Interim Treatment Guidelines for COVID-19 (Version 1.0, dated 2 April 2020) - available at: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx
	Interferon Beta-1B	250 microgram (8.0 million IU), contained in 1 ml of the reconstituted solution, to be injected subcutaneously every other day up to 7-14 days (3-7 doses).	Singapore National Center for Infectious Diseases, Interim Treatment Guidelines for COVID-19 (Version 1.0, dated 2 April 2020) - available at: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx
	Hydroxychloroquine	400 mg BD x 1 day (loading dose) followed by 200 mg bd for a 4 further days	Singapore National Center for Infectious Diseases, Interim Treatment Guidelines for COVID-19 (Version 1.0, dated 2 April 2020) - available at: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx
	Tocilizumab	To discuss with Rheumatology-Allergy-Immunology / Infectious Diseases /Intensive Care Physicians	Singapore National Center for Infectious Diseases, Interim Treatment Guidelines for COVID-19 (Version 1.0, dated 2 April 2020) - available at: https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx

<p>China</p>	<p>(4) Antiviral therapy: α-interferon (5 million U or equivalent for adult, add 2ml of sterile water, 2 times daily inhalation), lopinavir/ritonavir (200 mg/50 mg/capsule, 2 capsules each time for adults, twice a day, the course of treatment should not exceed 10 days). Ribavirin (combination with interferon or lopinavir/ritonavir is recommended, 500 mg each time for adults, 2 to 3 times intravenous infusions per day, the course of treatment should not exceed 10 days), chloroquine phosphate (for adults whose weigh over 50 kg, 500 mg each time, twice daily for 7 days; for those whose weigh less than 50 kg, 500 mg each time, twice daily for day 1 and day 2, once daily for day 3- day 7), Abidol (200 mg each time, three times a day for adults, the course of treatment should not exceed 10 days) can be tried. Attention should be paid to the adverse reactions of the above drugs, contraindications (such as chloroquine should not be used in patients with heart disease), and interaction with other drugs. It is not recommended to use 3 or more antiviral drugs at the same time. The use of related drugs should be stopped when intolerable side effects occur. The treatment of pregnant women should consider the number of weeks of gestation and choose drugs that have less impact on the fetus.</p>		<p>Chinese Clinical Guidance for COVID-19, available at: http://kfy.meetingchina.org/msite/main/cn</p>
<p>Japan</p>	<p>Lopinavir and Ritonavir</p>	<p>400 mg / 100 mg twice a day</p>	<p>Concept of antiviral treatment for COVID-19 1st edition (February 26, 2020), available at: http://www.kansensho.or.jp/modules/topics/index.php?content_id=31</p>
	<p>1) Pyrazinamide, 2) Repaglinide, 3) Theophylline 4) famciclovir, 5) sulindac</p>	<p>Use with caution</p>	<p>Concept of antiviral treatment for COVID-19 1st edition (February 26, 2020), available at: http://www.kansensho.or.jp/modules/topics/index.php?content_id=32</p>
	<p>Remdecib, Interferon, chloroquine</p>	<p>Not recommended yet</p>	<p>Concept of antiviral treatment for COVID-19 1st edition (February 26, 2020), available at: http://www.kansensho.or.jp/modules/topics/index.php?content_id=33</p>

COVID-19 Treatments under development as of April 20th

Active substance	Company/ies	Phase of clinical trial	Countries	Comments
Lopinavir/ritonavir (Kaletra)	AbbVie	Phase 3	Several in Europe and US	
Hydroxychloroquine or chloroquine	Several generics	Phase 3	Multiple sites in Europe, China and US	Side effects such as arrhythmias and haemolysis if G6PD deficient
ASC-09 + ritonavir	Ascleptis pharma	Phase 3	China	
Tocilizumab (Actemra)	Genetech/Roche	Phase 3	Multiple sites	
Favipiravir (Avigan)	Fujifilm	Phase 3	Multiple sites	
Remdesivir	Gilead	Phase 3	China, Japan, US and other sites	
Sarilumab (Kevzara)	Regeneron/Sanofi	Phase 3	US	
Leronlimab (PRO 140)	CytoDyn	Phase 2b/3	US	Study 1. For severely ill to critical patients Study 2. For mild to moderate patients
Ifenprodil	Algernon	Phase 2	South Korea	
APN01	Apeiron	Phase 2	Austria, Germany, Denmark	
Baricitinib ?other name for ritonavir		Recruiting for a phase 3 trial	US	Danger of thromboembolism

References

1. **AHA/ASA Journals** – *Association of Inpatient Use of Angiotensin Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers with Mortality Among Patients With Hypertension Hospitalized With COVID-19*
2. **ASHP Pharmacists Advancing Healthcare** - *Assessment of Evidence for COVID-19-Related Treatments: Updated 4/24/2020*
3. **BBC News**
4. **Clinical Trials Arena** - *Coronavirus treatment: Vaccines/drugs in the pipeline for COVID-19, 30 MARCH 2020*
5. **CureVac** - *CureVac focuses on the development of mRNA-based coronavirus vaccine to protect people worldwide*
6. **Elsevier Journal** – *COVID-19 Drug Therapy- Potential Options*
7. **Euronews-** *Racing for a cure: where are we with COVID-19 vaccines and treatments?*
8. **Genetic Engineering & Biotechnology News** - *How to Conquer Coronavirus: Top 35 Treatments in Development, by Alex Philippidis, March 2, 2020*
9. **JAMA** – *Clinical JAMA, Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)*
10. **KeAi Chinese Roots Global Impact** - *Recommended prophylactic and management strategies for severe acute respiratory syndrome coronavirus 2 infection in transplant recipients*
11. **New England Journal of Medicine** - *Perspective, Developing Covid-19 Vaccines at Pandemic Speed*
12. **Pan American Journal of Public Health** - *Clinical trials on drug repositioning for COVID-19 treatment*
13. **Pharmacy Times** - *Potential Pipeline Medications May Help Patients With Novel Coronavirus, 2020-03-11*

14. **Springer Open** - *Therapeutic strategies for critically ill patients with COVID-19*
15. **STAT news** - *WHO to launch multinational trial to jumpstart search for coronavirus drugs*
16. **World Health Organisation (WHO)** – *Landscape analysis of therapeutics as 21st March 2020*
17. **WHO R&D Blueprint** - *Nnovel Coronavirus An international randomised trial of candidate vaccines against COVID-19, 09 April 2020*
18. **World Health Organisation (WHO)** - *DRAFT landscape of COVID-19 candidate vaccines – 11 April 2020*
19. **World Health Organisation (WHO)** - *DRAFT landscape of COVID-19 candidate vaccines – 11 April 2020*

