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EMERGING THERAPEUTICS

Coronavirus Disease 2019 (COVID-19) – Searching for Safe and Effective Vaccines

Updated: November 9, 2020

Summary

Controlling the spread of Coronavirus 19 (SARS-CoV-2, COVID-19) through direct or indirect immunity will be important for society to mitigate the global pandemic, which was declared by the World Health Organization (WHO) on March 11, 2020. Vaccines offer indirect protection by working with your body to imitate disease and produce natural immunity. While over 100 vaccines are currently in development, none of them have been approved by the U.S. Food and Drug Administration (FDA). Realistically, commercial availability of a vaccine is likely at least 12 to 18 months away. However, as development of therapies for COVID-19 is rapidly evolving, we will update this document to include significant new information as it arises.

Highlights

- Coronavirus disease 2019 (COVID-19) is an infection from a new strain of coronavirus that has been associated with respiratory symptoms, including progression to acute respiratory distress syndrome (ARDS) and death in some patients.
- Currently, no approved vaccines treat or prevent COVID-19.
- More than 100 vaccines are in early clinical development with several options expected to reach clinical trials within months.
- Experimental use of vaccines deemed safe and effective may be rolled out to high-risk groups, such as healthcare workers, as early as summer of 2020.
- Commercial availability of a vaccine is still likely at least 12 to18 months away. Typically, a vaccine takes 10 years to develop. However, the COVID-19 pandemic is challenging the science, scale and speed at which traditional vaccines are being developed.
- As development of therapies is rapidly evolving, we will update this document frequently to provide the latest available information on potential vaccines for COVID-19

Vaccines

Vaccines are important to prevent infection and limit the spread of dangerous diseases. Immunity to a contagious disease often is achieved after successfully overcoming an infectious pathogen and developing T-lymphocytes or "memory cells" against it. Whenever that specific pathogen is encountered again, T-lymphocytes recognize it and activate B-lymphocytes to produce antibodies that prevent the disease from reoccurring. By introducing small amounts of the pathogen's proteins, vaccines generate an immune response without causing disease or infection. When a high percentage of the population develops immunity to a pathogen, either through recovering from infection, being vaccinated or a combination of both, the infection is less likely to spread from person to person. The resulting "community" or "herd immunity" is central to protect vulnerable patients, such as those who are immunocompromised, infants and the aging population.

FDA and Government Actions

To help expedite the availability of therapies for COVID-19, the FDA has loosened the process for vaccines to enter the market. An Emergency Use Application (EUA) can be issued to permit the use, based on scientific data, of medical products that may be effective for the diagnosis, treatment or prevention of a disease or condition when the U.S. Department of Health and Human Services (HHS) determines that a public health emergency has a

significant potential to affect national security or the health and security of U.S. citizens. Recently, HHS issued a EUA to increase the availability of additional diagnostic tests for the SARS-CoV-2 virus, and the production of ventilators.

Vaccines in Development

Several vaccines are in early-phase development to protect against COVID-19. Once they reach human clinical trials, data will be collected over at least six months to determine if the vaccines are both safe and effective for preventing infection with SARS-CoV-2. FDA will accelerate development for the more promising vaccines through its approval process. However, while the first vaccine is not expected to be commercially available for at least 12 months, experimental use products that show promise of being safe and effective could be rolled out to high-risk groups, such as healthcare professionals, as early as the summer of 2020. For comparison, typical vaccine development can take 10 years as the product advances from the lab, through animal testing and finally into the multiple stages of human clinical trials that support the safety and efficacy of the vaccine. The COVID-19 pandemic is challenging the science, scale and speed at which the vaccines are being developed. Table 1 includes examples of vaccines currently in development for COVID-19.

Investigational COVID-19 Vaccines

Vaccine	Manufacturer	Route	Status
mRNA-1273	Moderna	Intramuscular (two doses)	Phase 3
Ad26.COV2.S	Jansenn	Unspecified	Phase 3
NVX-CoV2373	Novavax	Unspecified	Phase 3
ChAdOx1 nCoV-19	Oxford/AstraZeneca	Intramuscular	Phase 2/3
BNT-162	Pfizer/BioNTech	Intramuscular	Phase 2/3
Coronavirus Vaccine	Sanofi/GlaxoSmithKline	Unspecified	Phase 1/2
INO-4800	Inovio	Intradermal	Phase 1
AdCOVID™	Altimmune	Intranasal (one dose)	Phase 1
Coronavirus Vaccine	CureVac	Intramuscular (one to three doses)	Preclinical
COVID-19 S-Trimer	GlaxoSmithKline/Clover	Unspecified	Preclinical

Express Scripts' Recommendations

Currently, no vaccines are FDA approved for the prevention of SARS-CoV-2 infections. According to the Centers for Disease Control and Prevention (CDC), the best mitigation is avoidance through social distancing, thoroughly washing hands, covering your mouth and nose while in public, covering coughs or sneezes, disinfecting frequently touched surfaces daily and isolating those with confirmed or suspected infections for at least 14 days.

Once a vaccine is approved and commercially available, Express Scripts will review the product for formulary status and make recommendations on coverage to the independent team of health professionals who form our P&T committee. As always, the Office of Clinical Evaluation and Policy will continue to monitor developments and provide updates as more information becomes available.

Stay up to date with the latest information regarding COVID-19 infections in the United States at:
https://www.cdc.gov/coronavirus/2019-ncov/index.html
https://www.nih.gov/health-information/coronavirus

Updates

Date	Vaccine	Comment
5.18.20	mRNA-1273 (Moderna) Phase 1 Results	Positive interim data was announced in a phase I study sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The study evaluated safety and immunogenicity for a total of 45 patients from 18 to 55 years of age. Participants were given one of three different intramuscular (IM) doses; 25µg, 100µg, and 250µg. Patients were given two doses; the first on day 1 followed by the second dose on day 29. Upon receiving the second injection, each patient will be monitored for an additional 12 months. A dose dependent immune response was seen in all three doses and COVID-19 specific antibodies were detected by day 15. By day 43, antibody results for the first four patients, in both the 25µg and 100µg, showed neutralizing antibody titers at or above levels generally seen in someone

		who has recovered from a COVID-19 infection. Ongoing studies will be amended to include a 50µg dose and include patients 55 years of age and older. The vaccine was generally safe and well tolerated. One participant at the 100µg dose experienced grade 3 redness at the injection site. The most serious adverse events occurred when three patients, all whom received 250µg dose, had grade 3 systemic symptoms. Grade 3 systemic symptoms occurred following the second injection and were self-limiting, resolving over time. An additional animal study was also provided to show replication of the virus was inhibited within the lungs of mice and provided full protection. Phase II trials are expected to begin soon while phase III trial protocols are finalized. The phase III trial is expected to start in July 2020. Moderna Announces Positive Interim Phase 1 Data for its mRNA Vaccine (mRNA-1273) Against Novel Coronavirus
6.30.2020	INO-4800 (Inovio) Phase 1 Results	Preliminary results were announced following two phase I studies, which Inovio plans to publish following peer review. In the trial, 40 healthy adults 18-50 years of age received two doses 28 days apart. Each patient had either a 1mg or 2mg dose via intradermal administration using the Inovio CELLECTRA 2000®. Overall 10 individuals reported adverse events that were localized and considered grade 1 injection site reactions. Immune response rates were observed in 94% of eligible participants analyzed, although levels for binding antibodies, neutralizing antibodies, and T-cell response were not reported. The company also reported that INO-4800 prevented viral replication in the lungs of mice and is undergoing similar testing in ferrets as part of the non-human primate (NHP) challenge for the U.S. Operation Warp Speed program. Inovio plans to increase its phase I study to include patients over 50 years of age and is seeking regulatory clearance for phase 2/3 trials this summer. INOVIO Announces Positive Interim Phase 1 Data For INO-4800 Vaccine for COVID-19
7.1.2020	BNT-162 (Pfizer/BioNTech) Phase 1/2 Results	Preliminary results of a placebo-controlled, observer-blind, dose-escalation phase 1/2 study have been announced for BNT-162 (Pfizer/BioNTech). BNT-162 is a lipid nanoparticle mRNA vaccine with a modified nucleoside. Forty-five patients between 18 and 55 years of age were assigned to dose arms of 10µg, 30µg, 100µg or placebo. The 100µg dose was given at day 1, only; the others were given at days 1 and 21. Due to severity of pain with the 100µg dose it was not repeated. Benefits were observed through day 35. Neutralizing antibodies and receptor binding domain (RBD) IgG levels showed a dose-dependent increase at each dosage level and upon the second injection. Two weeks after the second dose, plasma concentrations of RBD binding IgG and neutralizing antibodies from study participants were compared to samples of convalescent plasma from patients who have recovered from COVID-19. After the two-dose regimens the RBD-binding IgG concentrations were eight to 50 times greater and neutralizing antibodies were 1.8 to 2.8 times greater in plasma of vaccinated individuals. Although the 100µg cohort was not repeated, it provided no considerable benefit following the first dose. Pain at the injection site was the most common adverse event (AE) with all actively treated patients reporting pain with one or both injections. Systemic AEs included fever, chills and body aches, which all resolved within seven days. Except for one severe case of pain at the 100µg dose, all AEs were considered mild to moderate. Investigators plan to monitor for safety and efficacy for six to 24 months. Assuming that natural infection provides immunity to COVID-19, then the stronger vaccine response also could provide protection that warrants further investigation. Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report
7.20.2020	ChAdOx1 nCoV-19 or AZD-1222 (AstraZeneca/University of Oxford) Phase 1/2 Results	Preliminary results of a blinded, randomized phase I/2 study have been announced for AZD-1222 (AstraZeneca/University of Oxford). AZD-1222 is a vaccine made from a chimpanzee "common cold" adenovirus vector re-engineered to contain genetic information from the COVID-19 virus's spike protein. The study enrolled 1,077 healthy adults between 18 and 55 years of age. One-half of the participants received one dose of AZD-1222 at 5 x 10^{10} viral particles and one-half got a meningococcal vaccine, MenACWY, as a control. Ten participants received a second dose of AZD-1222 one

		month after the first. At both two weeks and two months following the AZD-1222 injection, all participants receiving it had an increased response in white blood cells known as T-cells. Some evidence indicates that patients who contract COVID-19 but remain asymptomatic have a sizeable T-cell response without an increase in anti-COVID-19 antibodies. For 91% of treated patients, one injection of AZD-1222 produced neutralizing antibodies at the level of a patient who has recovered from COVID-19. All ten participants who had two doses of AZD-1222 produced additional neutralizing antibodies. The most common AEs were temporary pain at the site of injection, mild headache, fatigue, chills, fever and body aches, which all were treatable with non-prescription pain relievers. Investigators plan to follow up with patients at six months and one year. Phase 2/3 clinical trials are being conducted to confirm results and to study different dosages and effectiveness for other age groups. Safety and Immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of phase 1/2, single blind, randomized controlled trial
9.9.2020	ChAdOx1 nCoV-19 or AZD-1222 (AstraZeneca/University of Oxford) Phase III – Voluntary Clinical Hold Announced	On September 9, 2020, AstraZeneca announced a voluntary clinical hold on the United Kingdom (U.K.) Phase III trial for AZD-1222 following an independent standard review that was prompted following an unexplained illness. Statement on AstraZeneca Oxford SARS-CoV-2 vaccine, AZD1222, COVID-19 vaccine trials temporary pause
9.12.2020	ChAdOx1 nCoV-19 or AZD-1222 (AstraZeneca/University of Oxford) Phase III – Trial Resumed	On September 12, 2020, AstraZeneca announced that they have resumed the U.K. Phase III trial for AZD-1222 following a voluntary clinical hold. COVID-19 vaccine AZD1222 clinical trials resumed in the UK
9.25.2020	Ad26.COV2.S Phase I/2a Study Results, Initiates Phase III Study.	On September 25, 2020, Johnson & Johnson reported preliminary results of its double blind, randomized, placebo-controlled phase I/IIa trial demonstrating that its COVID-19 vaccine triggered an immune response. The study evaluated a single dose and a two-dose schedule, separated 56 days apart, in healthy adults 18-55 years of age and healthy adults over 65 years of age. At 29 days post administration, detectable neutralizing antibodies was observed in 98% of participants. A significant T-cell and Th1 response was observed in subsets of patients believed to show immune protection against the disease. Adverse events (AEs) occurred in 64% of healthy adults and 36% of healthy adults over 65 years old. The most common AEs included fever, injection site pain, fever, muscle aches, fatigue and headache. The company indicated that safety and immunogenicity after one dose provided significant benefit and would warrant further study. Earlier, on September 23, 2020, Johnson & Johnson announced the start of its Phase III study evaluating safety and efficacy of a single dose vaccine vs. placebo in 60,000 adults 18 years of age and older. Preliminary Results for Phase I/IIa Study on COVID-19 Vaccine
10.13.2020	Temporary Pause on Johnson & Johnson's Phase III Ad26.COV2.S Vaccine Trial	On October 13, 2020, Johnson & Johnson announced that it is pausing all of its COVID-19 vaccine trials temporarily while it investigates an unexplained illness. An independent Data Safety Monitoring Board (DSMB) will evaluate the illness along with internal physicians. The study pause was due to the company's pre-determined safety protocols, not a regulatory body. Johnson & Johnson Temporarily Pauses Phase III Trial
10.23.2020	ChAdOx1 nCoV-19 or AZD-1222 (AstraZeneca/University of Oxford) Phase III – Trial Resumed in the U.S.	On October 23, 2020, AstraZeneca announced that they have resumed the U.S. Phase III trial for AZD-1222 following a voluntary clinical hold. ChAdOx1 nCoV-19 or AZD-1222 (AstraZeneca/University of Oxford) Phase III - Trial Resumed in U.S.

10.23.2020	Johnson & Johnson Phase III Ad26.COV2.S – Trial Resumed in the U.S.	On October 23, 2020, Johnson & Johnson announced they have resumed the U.S. Phase III trial for Ad26.COV2.S following a voluntary clinical hold. Johnson & Johnson Phase III - Trial Resumed in the U.S.
11.9.2020	BNT-162 (Pfizer/BioNTech) Preliminary Phase III Results	On November 9, 2020, Pfizer and BioNTech announced that early study results from a Phase III trial evaluating BNT-162. Data show the vaccine to be more than 90% effective at preventing COVID-19 – exceeding the FDA's minimum requirement for at least 50% efficacy for a COVID-19 vaccine. To date, the Phase III trial has enrolled 43,538 patients with almost 90% of patients receiving their second (final) dose. Up to 42% of participants in the trial are from an ethnically diverse background and 40% of participants are over 55 years of age. The trial is still enrolling patients until 164 confirmed COVID-19 cases have occurred. An independent Data Monitoring Committee (DMC) reviewed efficacy analysis on November 8, 2020. To date, the total confirmed COVID-19 case count is at 94 patients and the difference between vaccinated patients and those receiving placebo indicates at least 90% efficacy. The DMC did not report any serious safety concerns. The FDA has specified safety guidance for Emergency Use Authorization (EUA) at a medium of two months of data following second dose administration, which the company expects to reach by the third week of November. If BNT-162 is approved, as many as 50 million doses should be available this year with an additional 1.3 billion doses ready in 2021. BNT-162 (Pfizer/BioNTech) Preliminary Phase III Results

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