Chairman Clyburn, Ranking Member Scalise, and Members of the Select Subcommittee:

Thank you for the opportunity to discuss the role of the National Institute of Allergy and Infectious Diseases (NIAID) in the research response to coronavirus disease 2019 (COVID-19) and its etiologic agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within the Department of Health and Human Services (HHS) and the National Institutes of Health (NIH), NIAID is responsible for conducting and supporting basic and clinical research on emerging and re-emerging infectious diseases, including COVID-19. As the Director of NIAID and the Chief Medical Advisor to the President, I am pleased to discuss NIAID's research addressing this pandemic.

COVID-19 is a once-in-a-lifetime global infectious disease pandemic requiring an unprecedented public-private research effort. NIAID plays a central and important role in the public health response to COVID-19. NIAID has capitalized on decades of investment in fundamental basic research, including groundbreaking structure-based vaccine design at the NIAID Vaccine Research Center (VRC); engaged domestic and international research infrastructure; and leveraged highly productive partnerships with industry and longstanding relationships with community partners. NIAID utilized its existing domestic and international clinical trials infrastructure, originally established to conduct research on HIV and influenza, and worked with partners in the public and private sectors to establish the COVID-19 Prevention Network (CoVPN). The CoVPN has supported multiple COVID-19 vaccine candidates to progress in record time from concept to authorization for emergency use by the U.S. Food and Drug Administration (FDA). NIAID also has built on its longstanding relationship with community partners to successfully conduct these crucial clinical trials. NIAID initiated clinical trials with creative and adaptive designs, allowing the evaluation of multiple new and existing therapeutics for use against COVID-19. Several of these trials provided evidence of safety and efficacy of COVID-19 therapeutics and helped support authorization by the FDA.

These successes have helped slow the progression of the Tc 0.002 TSe (t)]Te n-2 (as b-2 (oe0.003 agr)-b (l)

Middle East respiratory syndrome coronavirus (MERS-CoV), using a double mutation known as S2P. This key finding facilitated the design of vaccine candidates that generate robust immune responses against coronaviruses and other viruses of public health importance such as respiratory syncytial virus. As soon as the sequence of SARS-CoV-2 was made available in January 2020, VRC researchers rapidly generated a stabilized SARS-CoV-2 spike protein for use in COVID-19 vaccine development. This crucial breakthrough in structure-based vaccine design for coronaviruses has led to the development of safe and effective COVID-19 vaccine candidates across a range of vaccine platforms.

Five candidate COVID-19 vaccines have entered Phase 3 clinical trials in the United States thus far, and three subsequently received EUAs from the FDA. Clinical trials to test COVID-19 vaccine candidates in pediatric populations are ongoing. On December 11, 2020, based on data from a Pfizer-supported Phase 3 clinical trial, an investigational vaccine developed by Pfizer and BioNTech became the first to receive an EUA from the FDA for the prevention of COVID-19 in individuals 16 years of age and older. NIAID has helped to advance four additional COVID-19 vaccine candidates through support for research on the foundational biology underlying the vaccine concepts, as well as for clinical testing through the CoVPN. Two of these vaccine candidates from Moderna, Inc., and Johnson & Johnson/Janssen have received EUAs.

Utilizing the CoVPN, NIAID is participating in the implementation of harmonized protocols a-62(a)-1 (-62(an2 (n(e)-1 (d)l)TJ)TJ)TJ

acceptance and vaccine hesitancy, NIH established the Community Engagement Alliance Against COVID-19 Disparities (CEAL) initiative, led by the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities. CEAL brings together trusted community leaders to serve as champions who share information about the importance of participating in COVID-19 research and communicate data on the safety and efficacy of authorized COVID-19 vaccines.

mRNA-1273 (Moderna)

As part of a longstanding collaboration, the NIAID VRC worked with the biotechnology company Moderna to develop a vaccine candidate designated as mRNA-1273, which uses a messenger RNA (mRNA) vaccine platform to express the stabilized SARS-CoV-2 spike protein. Early clinical trials demonstrated that mRNA-1273 was generally well tolerated and induced robust immune responses in healthy adults. NIAID and BARDA then began working with Moderna on a Phase 3 clinical trial through the CoVPN that showed that mRNA-1273 was 94.1 percent efficacious in preventing symptomatic COVID-19. On December 18, 2020, after a thorough review of comprehensive data on mRNA-1273, the FDA issued an EUA for the mRNA-1273 vaccine for prevention of COVID-19 in individuals 18 years of age and older. In subsequent observational studies under "real-world" conditions in broader segments of the population, mRNA-based vaccines continue to display a high level of effectiveness. In a recent article published in Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention (CDC) researchers and their collaborators showed that among health care personnel, first responders, and other essential workers, the mRNA-1273 and the Pfizer-BioNTech mRNA vaccine were 90 percent effective against SARS-CoV-2 infections 14 or more days after receiving a second dose.

Ad26.COV2.S (Johnson & Johnson/Janssen)

Decades of NIAID support for basic, pre-clinical, and clinical research on adenovirus (Ad)-based HIV vaccines underpin the development by Johnson & Johnson/Janssen of a coronavirus vaccine based on the Ad26-vector, known as Ad26.COV2.S or JNJ-78436735. NIAID is supporting a Phase 3 clinical trial of Ad26.COV2.S through the CoVPN and has provided immunological testing of the candidate using NIAID-us6735. of a coTj6 103.02 195.3 Tm[(D)3 (e01 Tw [e.3 0 Tip

moderate to severe/critical COVID-19 occurring at least 28 days after vaccination and 85 percent effective overall in preventing severe/critical COVID-19 across several geographical regions, including areas where emerging viral variants predominate. In the United States, the efficacy against moderate to severe/critical disease 28 days after vaccination with Ad26.COV2.S was 72 percent. On February 27, 2021, the FDA issued an EUA for Ad26.COV2.S for prevention of COVID-19 in individuals 18 years of age and older. On April 13, 2021, out of an abundance of caution, the FDA and CDC released a joint statement recommending a pause in the use of Ad26.COV2.S in order to review extremely rare case reports of blood clots after vaccine administration.

Other COVID-19 Vaccine Candidates

NIAID, through the CoVPN, is supporting Phase 3 clinical trials of COVID-19 vaccine candidates from AstraZeneca (AZD1222) and Novavax (NVX-CoV2373). AstraZeneca's AZD1222 COVID-19 vaccine candidate uses a chimpanzee adenovirus-vectored vaccine approach developed by researchers at the University of Oxford in collaboration with scientists at NIAID's Rocky Mountain Laboratories. On March 25, 2021, AstraZeneca announced an updated interim analysis of AZD1222 that reported that the vaccine candidate was 76 percent effective at preventing symptomatic COVID-19, including 85 percent effective in participants aged 65 years and over. Importantly, the efficacy of AZD1222 against severe COVID-19 disease was reported to be 100 percent. AstraZeneca has indicated it soon plans to submit a request for an EUA from the FDA, which will evaluate the clinical trial data for AZD1222.

Clinical Trials of COVID-19 Vaccine Candidates in Special Populations

To effectively end the COVID-19 pandemic, it will be important to vaccinate as many p

collaboration with NIAID and BARDA, announced the launch of KidCOVE, a Phase 2/3 study to evaluate the safety and efficacy of mRNA-1273 in children ages 6 months to less than 12 years. This study is in addition to Moderna's ongoing TeenCOVE study of mRNA-1273 in adolescents between the ages of 12 and 17. Other vaccine developers also have begun, or are planning to begin, trials to test their vaccine candidates in children, adolescents, and other special populations.

Monoclonal Antibodies to Prevent COVID-19

NIAID scientists, collaborating with Regeneron Pharmaceuticals and Eli Lilly and Company, also initiated two Phase 3 clinical trials to evaluate whether their investigational monoclonal antibodies, known as REGEN-COV and bamlanivimab respectively, can prevent infection or symptomatic disease in people at high risk of exposure due to their living or working conditions. Each company recently reported promising initial results, and further analysis of the data from the trials is ongoing.

Identifying Therapeutics to Treat COVID-19

Safe and effective therapeutics are urgently needed to treat patients with COVID-19. NIAID launched a multicenter, randomized placebo-controlled clinical trial, the Adaptive COVID-19 Treatment Trial (ACTT), to evaluate the safety and efficacy of multiple investigational therapeutics for COVID-19. ACTT-1 examined the antiviral drug remdesivir for treatment of severe COVID-19 in hospitalized adults. Based on positive data from ACTT-1, the FDA approved the use of remdesivir for treatment in adults and children 12 years of age and older and weighing at least 40 kg hospitalized due to COVID-19. ACTT-2 evaluated the anti-inflammatory drug baricitinib in combination with remdesivir, and based on favorable data from ACTT-2, the FDA issued an EUA for the use of baricitinib in combination with remdesivir for treatment of adults and children older than 2 years hospitalized with COVID-19 and requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation. ACTT-3 is currently evaluating treatment of patients hospitalized with COVID-19 with remdesivir plus interferon beta-1a, which is used to treat individuals with multiple sclerosis. ACTT-4 is currently enrolling adults hospitalized with COVID-19 to assess baricitinib plus remdesivir versus the glucocorticoid dexamethasone plus remdesivir.

NIAID, in collaboration with other NIH Institutes, also launched two clinical trials as part of the ACTIV partnership, which utilizes master protocols allowing the addition of other

investigational therapeutics as the trials continue. The two studies, ACTIV-2 and ACTIV-3, initially evaluated the use of the monoclonal antibody bamlanivimab to treat COVID-19 in outpatient and inpatient settings, respectively. Bamlanivimab was discovered by the company AbCellera in collaboration with the NIAID VRC and developed by Eli Lilly. Bamlanivimab received an FDA EUA in November 2020 for treatment of mild-to-moderate COVID-19 in patients with high risk for COVID-19 disease progression, based on data from a Lilly-sponsored Phase 2 clinical trial. ACTIV-2, which is focused on outpatients, has since been expanded to evaluate a combination monoclonal antibody therapy, BRII-196 and BRII-198, as well as three investigational therapeutics: SNG001, an inhalable beta interferon; AZD7442, an investigational long-acting antibody combination; and camostat mesilate, an orally administered molecule that may block SARS-CoV-2 from entering cells. ACTIV-3 currently is evaluating the AZD7442 monoclonal antibody combination in hospitalized patients. In addition, NIAID launched a Phase 3 trial called, "Inpatient Treatment with Anti-Coronavirus Immunoglobulin," or ITAC, to evaluate hyperimmune intravenous immunoglobulin for treatment of COVID-19 in hospitalized adults. NIAID also began a Phase 3 CoVPN trial of an Eli Lilly combination therapy, bamlanivimab and etesevimab, for treatment of mild to moderate COVID-19. In separate studies, NIAID-supported scientists and collaborators are evaluating the potential impact of emerging SARS-CoV-2 variants on the efficacy of monoclonal antibodies. The FDA now includes information on the susceptibility of SARS-CoV-2 variants in its fact sheets for health care providers for each of the monoclonal antibody therapies currently available through an EUA. In particular, the FDA notes that in areas where SARS-CoV-2 variants resistant to bamlanivimab alone are circulating, health care providers can mitigate the risk of treatment failure by using other authorized monoclonal antibody therapies.

NIAID also announced the ACTIV-5/Big Effect Trial (BET), which is designed to streamline the identification of experimental COVID-19 therapeutics that demonstrate the most promise. BET, an adaptive Phase 2 clinical trial, compares different investigational therapies to a common control arm to identify treatments with relatively large effects as promising candidates for further study in large-scale trials. BET initially is evaluating two therapeutics: risankizumab, an immunomodulatory monoclonal antibody developed by Boehringer Ingelheim and AbbVie, which is FDA-approved for the treatment of severe plaque psoriasis; and lenzilumab, an investigational immunomodulatory monoclonal antibody developed by Humanigen.

The NIH also has established the COVID-19 Treatment Guidelines Panel to provide recommendations to health care providers regarding specific COVID-19 treatments based on the

best available science. The Guidelines also address considerations for special populations, including pregnant women and children. Each Treatment Guidelines section is developed by a working group of Panel members with expertise in the area addressed in the specific section; these members conduct systematic, comprehensive reviews of relevant information and scientific literature. The Panel comprises representatives of NIH and five other federal agencies along with representatives of nine professional organizations, academic experts, and treating physicians including providers from high COVID-19 incidence areas, and community representatives. The Panel meets regularly to evaluate possible treatment options for COVID-19 and update the Treatment Guidelines as new clinical evidence emerges.

Responding to Emerging Variants of SARS-CoV-2

NIAID is fully engaged in efforts to mitigate the potential impact of emerging variants of SARS-CoV-2. NIH, including NIAID, participates in the HHS-established SARS-CoV-2 Interagency Group, along with CDC, FDA, BARDA, the Department of Defense (DOD), and the U.S. Department of Agriculture to address the potential impact of emerging variants on critical SARS-CoV-2 countermeasures. NIH, CDC, and DOD are assessing whether vaccine-induced immunity, or natural immunity from prior infection, can be effective in combating the variants. NIH, BARDA, and DOD also are determining the efficacy of certain authorized therapeutics against emerging variants in cells and in animal models.

NIAID is collaborating with vaccine manufacturers on key areas of research to investigate whether vaccines designed for the original strain of SARS-CoV-2 could maintain efficacy against emerging variants. NIAID also is conducting and supporting comprehensive studies to understand the ability of vaccine-induced antibodies to neutralize the variant viruses. NIAID researchers analyzed the immune responses of individuals who recovered from COVID-19 prior to the emergence of variants and demonstrated that T cells – a key component of the immune response to SARS-CoV-2 – were also capable of recognizing the three most widespread SARS-CoV-2 variants, B.1.1.7, B.1.351, and P1. These findings, published in Open Forum Infectious Diseases, shed new light on the role of T cells in the development of immunity to SARS-CoV-2 and suggest that these cells also may help protect against emerging variants of concern. On March 25, 2021, NIAID launched a Phase 1 clinical trial in healthy adults to assess the safety and immunogenicity of second-generation COVID-19 vaccine candidates developed by Gritstone Oncology, Inc. Gritstone's COVID-19 vaccine candidates utilize a strategy aimed at inducing both neutralizing

antibodies and T cell responses to elicit a broad immune response. This approach could provide protection against emerging SARS-CoV-

NIAID, along with FDA, is supporting a National Cancer Institute (NCI) effort to determine the sensitivity and specificity of certain SARS-CoV-2 serological tests, which can detect antibodies indicative of a prior exposure to SARS-CoV-2. NCI and NIAID also are working to establish a collaborative network to increase national capacity for high-quality serological testing with rapid return-of-results to subjects. These efforts include the use of serological testing to support clinical trials of convalescent serum and the establishment of registries for seroprotection studies. NIAID, NCI, the National Center for Advancing Translational Sciences, and the National Institute of Biomedical Imaging and Bioengineering are partnering on a study, called the Serological Sciences Network or SeroNet, to investigate whether adults in the United States without a confirmed history of SARS-CoV-2 infection have antibodies to the virus, thus indicating prior infection. The study is evaluating the durability of the immune response and aspects of the immune response that contribute to protection against COVID-19.

NIAID scientists are participating in leadership of the COVID Human Genetic Effort, an international consortium of hospitals and genetic sequencing hubs that aim to discover genetic factors conferring resistance to SARS-CoV-2 infection or predisposing to severe COVID-19 disease. The consortium has identified a subgroup of patients with severe COVID-19 that have ineffective immune responses to SARS-CoV-2, some of whom have identifiable mutations in key immune pathways. NIAID also supports efforts to understand the rare, but extremely serious, multisystem inflammatory syndrome in children (MIS-C) that has been associated with SARS-CoV-2 infection in children and adolescents. NIAID hosted a virtual workshop on MIS-C with scientists and clinicians from academia, NIH, FDA, and industry, and a report of the workshop recommendations was published on November 2, 2020. NIAID also supports the Pediatric Research Immune Network on SARS-CoV-2 and MIS-C (PRISM) to evaluate acute and long-term clinical and immunological effects of MIS-C and SARS-CoV-2 infection in children. In addition, NIAID is collaborating with Children's National Medical Center to follow 1,000 children with a history of SARS-CoV-2 infection, including those with MIS-C, to determine long-term effects of the illness. NIAID is participating in a trans-NIH effort to coordinate MIS-C research led by NHLBI and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. This centralized effort, the Collaboration to Assess Risk and Identify Long-term Outcomes for Children with COVID (CARING for Children with COVID), will permit data to be shared across studies to determine the spectrum of illness and predict long-term consequences of infection.