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Pathway to Protection: Expanding Availability of COVID-19 Vaccines

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Chairwoman DeGette, Ranking Member Griffith, and Members of the Subcommittee, I am Ruud Dobber, PhD, Executive Vice President BioPharmaceuticals Business Unit and President, North America, at AstraZeneca. I have been with Astra and, through its merger with Zeneca Group, AstraZeneca, since 1997, and I am responsible for product strategy and commercial delivery for cardiovascular, renal and metabolism, respiratory, and immunologic diseases, including our vaccine and long acting antibody. I am here today to convey AstraZeneca's strong commitment to ongoing efforts to develop and manufacture the AZD1222 vaccine candidate for the prevention of COVID-19. We greatly appreciate the opportunity to engage with you today on this important topic, and I hope to emphasize our dedication and commitment to delivering safe and effective solutions for fighting the COVID-19 pandemic in the United States and across the world.

AstraZeneca is a global, science-led biopharmaceutical company that focuses on the discovery, development, manufacturing, and commercialization of innovative medicines, primarily for the treatment of diseases in the following therapeutic areas: Oncology, Cardiovascular, Renal & Metabolism, and Respiratory and Immunology. We are proud to call Wilmington, Delaware home to our North American Headquarters, and that one of our three global R&D headquarters is located in Gaithersburg, Maryland. Overall, we have approximately 13,000 employees in the United States, with operations in 12 different states and Puerto Rico (California, Delaware, Indiana, Kentucky, Maryland, Massachusetts, New Jersey, New York, North Carolina, Ohio, Pennsylvania, and Texas), including eight manufacturing sites. These sites account for nearly one-third of our total manufacturing footprint. In addition to our U.S. presence, we have an additional 18 manufacturing sites throughout the rest of the world. In total, AstraZeneca operates in over 100 countries, and we are leveraging our global workforce and resources to address this worldwide crisis.

Today, I will focus on four key elements of AstraZeneca's development and manufacturing program for AZD1222:

- *First*, as previously conveyed to the Subcommittee in July 2020, our strategic approach for AZD1222 has focused on partnering with scientists, governments, multilateral organizations, like CEPI and GAVI, and manufacturers to establish agreements for the

development, supply, and distribution of the vaccine in an equitable manner across the world. AstraZeneca has entered into an exclusive licensing arrangement with the University of Oxford for the global development, production, and supply of AZD1222, which also includes vaccine redevelopment to combat variants of the virus. To support our goal of providing broad and equitable access as quickly as possible, we have entered into agreements with the United States and certain other governments and organizations, for supply of hundreds of millions of doses of our vaccine. The cost of the doses of the vaccine under those agreements will provide no profit for AstraZeneca. In addition to our vaccine efforts, we have also collaborated with the government and academia on the development of monoclonal antibodies for the prevention and treatment of COVID-19.

- *Second*, AstraZeneca is continuing to progress through global clinical trials to support the approval and emergency use authorization of AZD1222 in the U.S. and across the world. While clinical studies are ongoing, analyses and studies conducted to date indicate that AZD1222 is well tolerated and effective for the prevention of COVID-19. In addition, we have completed enrollment in our U.S. Phase III trial to support U.S. Food and Drug Administration ("FDA") authorization in the U.S.

- *Third*, prior to receiving authorization in the U.S., we began scaling up our manufacturing operations to manufacture the vaccine so that doses will be available in the U.S. upon emergency use authorization to avoid any delays. We operate our vaccine manufacturing operations in the U.S. at or near full capacity and are not currently experiencing significant material or equipment constraints.

- *Fourth*, AstraZeneca has initiated studies to address the emerging threats posed by new variants. Initial analyses, while still ongoing and subject to verification, suggest AZD1222 shows promise against the U.K. variant of the virus, and Oxford University is already developing next generation adenoviral vector vaccines incorporating the genetic changes to the spike protein found in the new Brazil and South Africa variants.

I. Collaboration

The progress that AstraZeneca has made in identifying and developing AZD1222 would not have been possible without our collaborations with academia and government agencies. These joint efforts have been essential in expediting the development program for the vaccine. As the Subcommittee is aware, our exclusive global development and distribution agreement with the Jenner Institute at the University of Oxford and the Oxford Vaccine Group gave AstraZeneca a license to develop and to distribute the University's novel recombinant adenovirus vaccine candidate AZD1222, formerly known as ChAdOx1 nCoV-19. Notably, this licensing agreement covers the redevelopment of the ChAdOx1 platform for variants of SARS-CoV-2.

We have also entered into two agreements with the U.S. government for the development, production, and supply of 300 million doses of AZD1222 should it receive authorization. The development program under these agreements includes a Phase III clinical trial with over 30,000 participants, which began in August 2020 and concluded enrollment in mid-January. Our

agreements with the U.S. government also include a pediatric program that is scheduled to begin in the coming months. We expect high level results from our Phase III trial soon, and, assuming a positive trial, we plan to file for emergency use authorization shortly thereafter. The U.S. government will own the doses of vaccine that we produce and will determine how the doses are distributed. We are very pleased that the U.S. government has moved with speed to advance critically important agreements and provide ongoing support to AstraZeneca, and I would like to take this opportunity to thank the U.S. government for its commitment to advancing these efforts.

II. Vaccine Development

Following rolling submission to regulatory authorities of data from our ongoing global clinical trials, we have received conditional marketing or emergency use authorization for AZD1222 in more than 50 countries. Phase II/III trials are ongoing in the U.K., U.S., Chile, Peru, and Brazil, while Phase I/II trials are ongoing in South Africa, Japan, and Kenya. The trials are collectively assessing efficacy, safety and immune responses in up to 60,000 participants across a broad age range and diverse racial, ethnic and geographic groups.

The primary analysis of the Oxford-led clinical trials from the U.K., Brazil, and South Africa, as detailed in a recent paper submitted for publication, indicated that AZD1222 is well tolerated and effective at preventing COVID-19 based on 17,177 participants. Patients in these studies generally received two doses of AZD1222 in dosing intervals ranging from four weeks to over 12 weeks. The analysis found the vaccine was 100% protective against severe disease, hospitalization and death more than 22 days after the first dose, was 76% effective overall three weeks after the first dose that is maintained to the second dose, and could result in a reduction in disease transmission of up to 67%. In addition, the primary analysis of overall vaccine efficacy at more than 14 days after the second dose was approximately 67%. The analysis also showed that efficacy increased up to 82% with a longer inter-dose interval of at least 12 weeks or more. It is possible that increasing the interval between doses could potentially allow more people to be vaccinated in the first instance, as well as maximize efficacy after two doses. Accordingly, we are discussing with regulators how best to investigate this further.

The ongoing Phase III trial in the U.S. is a randomized, double-blind, placebo-controlled multicenter study assessing safety, efficacy and immune response of two doses of AZD1222 given 28 days apart in over 30,000 participants over the age of 18 years across 100 sites. In addition to sites in the U.S., this trial was extended to sites across Chile and Peru. Trial participants who were healthy or had medically-stable chronic diseases and were at increased risk for exposure to the SARS-CoV-2 virus and COVID-19 were randomized in a 2:1 ratio of AZD1222 to placebo. This ratio was intended to increase the number of participants receiving the vaccine and, therefore, increase the size of the safety database that supports approval and authorization.

To help ensure confidence in use of AZD1222 in diverse patient populations, participants in this trial include diverse racial and ethnic groups who are healthy or have stable underlying medical conditions. We have worked with the National Institute of Allergy and Infectious Diseases' new clinical trials network to recruit and enroll participants in communities where there is a strong minority representation, including African American, Hispanic, and Native American populations. We have also worked closely with principal investigators at study sites to achieve

enrollment across diverse populations in all age groups and all populations older than 65 years of age.

We are happy to report that recruitment for this trial is now complete. Because availability of the data will be based on local spread of the disease, we cannot reliably predict the timing of data readouts. However, because the attack rate has been high, we are hopeful that the readout of the data will be available in the coming weeks. These data will be submitted to the FDA when they become available. It is important to mention that the dosing interval used in this trial is four weeks, which may not maximize efficacy. In the UK, a vaccination strategy based on a three month dosing interval is underway and real world evidence should become available in the next few weeks, providing additional real life evidence of the impact of the vaccine in different cohorts of patients, including older patients.

At the heart of AstraZeneca's core values is to "follow the science" and establishing the safety and efficacy of the vaccine through rigorous science is of paramount importance. Although our development program is progressing rapidly, our submissions for authorization for AZD1222 to date have met the stringent requirements established by regulators around the world. Further, earlier this month, the World Health Organization Strategic Advisory Group of Experts issued interim recommendations for the use of AZD1222 against COVID-19. We have made efforts to ramp up manufacturing of the vaccine while increasing personnel and resources to enable quicker trial recruitment. Two independent Data and Safety Monitoring Boards oversee the studies to ensure safety and quality, such as by monitoring safety and efficacy results, evaluating cumulative safety and other clinical study data at regular intervals, and making appropriate recommendations based on the available data. In addition, the U.S. Phase III trial has a two-year follow up period to monitor participants for efficacy and safety. The other current clinical trials will monitor participants for efficacy and safety over 12 months, and we will continue to evaluate the need to extend these trials to monitor efficacy and safety over a longer duration.

III. Vaccine Manufacturing and Supply

As noted, even prior to any approvals or authorizations, we proceeded to ramp up manufacturing for our COVID-19 vaccine with the support of the U.S. and other governments. We made this decision so that the vaccine will be ready for distribution and administration as soon as possible following regulatory approval or emergency use authorization. In order to support our goal of producing billions of doses of the vaccine for markets around the world as safely and quickly as possible, we have built more than a dozen regional supply chains in parallel across the world with our partners to support broad and equitable access at no profit during the pandemic period and we continue to forge additional partnerships to deliver this commitment. Supply chains have been set up to meet the needs of specific government or multinational organization agreements and the vaccine produced from the supply chains are generally country or region specific and we have tried to prioritize local manufacturing wherever possible. Our supply chain includes multiple manufacturing facilities across each stage of production (*i.e.*, drug substance, drug product and finished packaging). While we have been challenged by lower yields in some parts of the world despite our best efforts, we continue to make progress with our U.S. supply chain, with the goal of supplying doses upon emergency use authorization. We are working closely

with the U.S. government to ensure transparency around our progress and challenges. We also appreciate the tremendous support received from BARDA along the way. We are not currently experiencing significant material or equipment constraints.

With respect to our U.S. supply chain, we are proud that the vaccines covered by our agreements with the U.S. government are being manufactured in the United States. We are conducting filling and packaging activities at our West Chester, Ohio site. In addition, we have partnered with other U.S. pharmaceutical contract development and manufacturing organizations to manufacture the drug substance and drug product for the vaccine as well as handle certain packaging operations. Our Operations and Procurement teams have worked to secure and accelerate a global supply chain of critical raw materials, reagents and consumables in collaboration with our suppliers. At this time, we have secured sufficient supply of vials and stoppers to support our internal global supply chain, based on 10 doses per vial. Syringes are being sourced directly by the government vaccination teams and we believe that the U.S., among others, has secured adequate supply. In addition, since the Defense Production Act Title I priority rating was put in place, our suppliers have not communicated any significant delays of materials or equipment. FDA site visits have been conducted at all of these sites to ensure the proposed manufacturing facilities were suitable for production and had appropriate controls in place.

Despite the speed in scaling up our manufacturing operations, safety and quality standards have been, and remain, of paramount importance. Numerous safety tests and quality control measures are carried out during the manufacturing process, including on the final packaged product. We have built an extensive analytical network and are rapidly transferring our analytical methods to these laboratories. The impact of factors such as heat, light, radiation, environmental changes as well as interaction with container materials have also been determined for the vaccine through testing. Storage and handling conditions are defined at each stage of the production process to optimize product stability, shelf life, and ensure safety and quality is maintained. Our vaccine can be easily stored, transported and handled at refrigerated conditions (2-8°C/36-46°F) for at least six months and administered within existing healthcare settings, which facilitates access and supply. We are also continually identifying and implementing new ways of working that will accelerate production of AZD1222 and reduce the time to reach communities while maintaining the highest standards of quality.

IV. Addressing SARS-CoV-2 Variants

AstraZeneca has initiated studies to address the emerging threats posed by new variants, especially the U.K. variant. Sub-analyses of the Phase II/III trial data in the U.K., which were published as a pre-print in *The Lancet* this month and are still ongoing and subject to verification, suggest that the vaccine's efficacy is similar in participants with the U.K. variant and in those without this strain. We are particularly encouraged by these results, as the Centers for Disease Control and Prevention and Dr. Anthony Fauci have hypothesized that this strain may become the dominant strain in the U.S. Early data from a small Phase I/II trial in South Africa conducted by a local expert in coordination with Oxford University, and studying AZD1222 in predominantly young, healthy adult participants with an average age of 31 years has shown limited efficacy against mild to moderate disease, primarily due to the South Africa variant. Importantly this

analysis was not statistically significant, and no conclusions could be drawn regarding efficacy in severe disease. It is well recognized that achieving protection against mild disease is a higher hurdle for a vaccine, and there is often a gradient of increasing efficacy from mild to severe disease. This has also been observed with vaccines against SARS CoV-2, including AZD1222. Hence, depending on the mix of case severities in a trial, different levels of efficacy may be observed. Efficacy against severe disease is, of course, the most important outcome measure for public health. The South African study was not able to properly ascertain efficacy against severe disease, given the participants were predominantly young, healthy adults with an average age of 31 years. No severe disease or hospitalizations were observed in vaccine or control participants. We are in communication with the South African Ministry of Health to support the evaluation of AZD1222 for use against severe disease and hospitalization caused by the South African variant.

The Oxford University platform technology can be adapted to help address challenges with the new variants, and our collaborators have already started developing the next generation adenoviral vector vaccines incorporating the genetic changes to spike proteins found in the new variants in Brazil and South Africa. Although the adenoviral vectored vaccine genetic code can be altered to match new variants quickly in the laboratory, additional steps will be required to ensure the quality and effectiveness of the new vaccine, and it is likely the process from start to finished product would take 8 to 9 months to complete. In addition, it will be important to test the effectiveness of the new vaccine against the new variants in a clinical trial. Given that we will have substantial safety data on the vaccine platform and there would be relatively small changes in the vaccine and its manufacturing, we are discussing a path forward with regulators globally. We welcome further discussions with the FDA and other regulators as part of the bigger picture of addressing vaccination needs going forward. Establishing a potential pipeline of future vaccines will be essential, and this can only be achieved in an efficient and effective manner with collaboration across industry and regulatory authorities globally.

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AstraZeneca is fully committed to fighting the COVID-19 pandemic, helping to save lives through the expedited, science-based development and manufacture of AZD1222 and other potential prophylactic and therapeutic options. Our team is continuing to make progress in our development and manufacturing programs, and we fully intend to provide broad access to AZD1222, if approved or authorized under an emergency use authorization, in the U.S. and across the world.

Chairwoman DeGette, Ranking Member Griffith, and Members of the Subcommittee, on behalf of AstraZeneca, thank you for the opportunity to participate in today's hearing. We appreciate your keen interest in these important issues, and I look forward to answering your questions.