Good afternoon. I'm Commander Ibad Khan, and I'm representing the Clinician Outreach and Communication Activity COCA with the Emergency Risk Communication Branch at the Centers for Disease Control and Prevention. I'd like to welcome you to today's COCA Call, Therapeutic Options to Prevent Severe COVID-19 in Immunocompromised People. All participants joining us today are in listen only mode.

Free continuing education is offered for this webinar. Instructions on how to earn continuing education will be provided at the end of the call. In compliance with continuing education requirements, CDC, our planners, our presenters and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. Planners have reviewed content to ensure there is no bias. This presentation will not include any discussion of the unlabeled use of a product or a product under investigational use except parts of the presentation will focus on monoclonal antibodies that are not FDA approved but are FDA authorized under emergency use authorizations EUA. And there will be mention of COVID-19 serology tests that have FDA EUAs and have been used for post-vaccine serology determinations for clinical trials and research studies, as noted in published or preprint articles. CDC did not accept commercial support for this continuing education activity.

At the conclusion of today's session, the participants will be able to accomplish the following: Describe FDA's role in issuing an EUA for casirivimab/imdevimab; outline the process for ordering and distributing casirivimab/imdevimab; discuss findings of studies on monoclonal antibodies for COVID-19 published or unpublished preprint; describe the National Institutes of Health COVID-19 Treatment Guidelines Panel's recommendations on using monoclonal antibodies to treat non-hospitalized patients with mild to moderate COVID-19; and list options for post-exposure prophylaxis use of casirivimab/imdevimab.

After the presentation, there will be a Q&A session. You may submit questions at any time during today's presentation. To ask a question using Zoom, click the Q&A button at the bottom of your screen, then type your question in the Q&A box. Please note we receive many more questions than we can answer during our webinars. If you're a patient, please refer your questions to your healthcare provider. If you're a member of the media, please contact CDC Media Relations at 404-639-3286. Or send an email to media@cdc.gov.

I would now like to welcome our presenters for today's COCA Call. We're pleased to have with us Dr. Elliott Raizes, who's the Task Force Lead for the Health Services and Worker Safety Task Force as part of CDC COVID-19 Response; Dr. Adi V. Gundlapalli, who is the Co-Lead of the Serology and Correlates of Protection Tiger Team as part of CDC's COVID-19 Response and the Chief Public Health Informatics Officer for CDC Center for Surveillance, Epidemiology and Laboratory Services. Dr. John Farley, who's the Director of the Office of Infectious Diseases in the Center for Drug Evaluation and Research in the Office of New Drugs at the FDA; Dr. Colin Shepard, who's a CDC liaison to the Assistant Secretary for Preparedness and Response; and Dr. Rajesh Gandhi, who's the Director of HIV Clinical Services and Education at Massachusetts General Hospital and a Professor of Medicine at Harvard Medical School.

It is my pleasure now to turn it over to Dr. Raizes. Dr. Raizes, please proceed.

Good afternoon. The US Food and Drug Administration has recently issued the emergency use authorization or EUA for monoclonal antibodies for both the treatment of COVID-19 and for post-exposure prophylaxis for certain patients, including patients with immunocompromising conditions. As you heard earlier, the purpose of today's call is for the Centers for Disease Control and Prevention to bring together federal agencies and experts from the field to speak on EUAs and limitations of authorized uses and to disseminate current information on the role of monoclonal antibodies for treatment and prevention, the process for ordering and distributing monoclonal antibodies and what we know about commercial serological testing for COVID-19 especially in the context of managing persons with immunocompromised conditions.

We will not be discussing vaccines, extra vaccine doses for persons with immunocompromising conditions. That will be discussed tomorrow at a meeting of the Advisory Committee on Immunization Practices, which you can access online. We hope that the speakers on this panel will answer many of your questions you have as healthcare providers and try to or -- as they try to support persons with these conditions in the context of ongoing community transmission of SARS-CoV-2. Next slide.

CDC strongly encourages clinicians, patients and their advocates and health system administrators to regularly consult the COVID-19 Treatment Guidelines published by the National Institutes -- Institutes of Health. The treatment and management recommendations in these guidelines are based on scientific evidence and expert opinion and are frequently updated. Thank you.

Now I'd like to introduce Dr. Gundlapalli. [Silence].

Dr. Gundlapalli, please check your mute button.

Yes, thank you. Can you hear me now?

Yes, sir. Please proceed.

Thank you. Apologies for that. Good afternoon or good morning, everyone, as the case may be. I appreciate being invited to this call; and thank you, Dr. Raizes, for the introductory remarks. Next slide, please.

Starting with the overview of SARS-CoV-2 serology going straight to commercially available SARS-CoV-2 binding assays, there are currently 87 such assays that have FDA emergency use authorization and are listed on the FDA website. Most of these assays are qualitative, in that they provide a reactive or non-reactive answer with regard to the presence of antibodies to SARS-CoV-2 in the blood specimen. Twelve are semi-quantitative and one is quantitative. These assays also provide a reactive or non-reactive answer, yes, no type of answer and then, if reactive, provide a numerical value of the amount of antibody present within a certain range. The current indication for these serology tests as stated in the EUA from FDA is for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2 indicating recent or prior infection. Next slide, please.

Looking at immune response to SARS-CoV-2 antigen-specific antibodies, the detection of antibodies acknowledges the significant and measurable end-product of the complex machinery of the adaptive immune system, as noted in the EUA for commercial assays. False positive results may occur. Knowledge of absence of antibodies is also informative. Disruptions in the adaptive immune response cascade can occur, and false negative results may also occur due to either antibody decay or assay performance.

Please note that none of the commercially available serology assays are FDA approved nor recommended for assessing protective immunity individuals. And there are two reasons for this. Established or accepted serologic correlates of protection are pending at this time, and only one quantitative IgG assay approved -- is approved for results that are traceable to an international standard. And that's needed to quantify and to compare results across labs and assays. Please note that host response also includes innate and cellular immune responses. Tests to perform or check for these immune responses are not usually that available commercially. Next slide, please.

Between two immune responses to COVID-19 vaccinations in immunocompromised people, the underlying immune compromise or therapies disrupt the adaptive immune response. Post-vaccines serological testing has been performed only as part of clinical trials or research studies, and clinical utility of post-vaccination serological testing has not yet been established. There is evidence of -- that continues to accumulate regarding the decrease in production of binding and neutralizing antibodies to COVID-19 vaccination in immunocompromised individuals. These were discussed in detail at a recent Advisory Committee on Immunization Practices or ACIP meeting on July 22, 2021. And those slides are publicly available.

There are wide ranges of response to vaccination, as noted by post-vaccination serology in these research studies, from -- all the way from near zero or lack of response to vaccination and below 20% for certain solid organ transplant patients to 40 to 50% of patients responding with those who have hematological cancers or immunosuppressive therapies and to near 95% response for some dialysis patients. For specific diagnoses and therapies that severely limits the variability of immune response so, again, so variability is noted in the immune response based on severity of underlying immunocompromise and therapy. Please note that in patients with immunocompromised cellular immune responses are also impaired. Next slide, please.

Speaking to a brief discussion on serological correlates of protection or as some folks are referring to these as correlates of risk for breakthrough infections, what we do know is that from limited publications on serology, vaccine effectiveness and breakthrough infections which have small sample sizes, individual studies, there is a consistent relationship between quantitative binding antibodies and neutralizing antibody levels. Neutralizing and binding antibodies will also correlate with protection or risk of breakthrough infection after vaccination in cohorts of individuals. There is a need for higher levels of neutralizing antibodies that has been shown in recent studies when looking at variants of concern such as Delta. And binding antibodies may be a practical solution looking at serological correlative protection as neutralizing antibodies are not readily available.

What we don't yet know are threshold levels or ranges to make a statement such as percent protection above a certain level or in this range of antibodies, and those data are not yet available. This will be challenging as the impact of variants on estimating and setting levels of antibodies for protection of risk has not been done yet. And there will be heterogeneity by age, race, ethnicity and immunocompromised status. Furthermore, how we could use those thresholds is also being discussed in clinical, scientific and public health communities.

As a recent preprint on this topic pointed out referenced later on in the slides, these correlates add to the body of knowledge toward establishing an immune market -- marker surrogate endpoint for COVID-19 vaccines and may be useful for bridging vaccine efficacy between vaccines that are authorized or approved based on clinical trial efficacy data and newer vaccines. These studies usually look at subsequent COVID-19 occurrence over three to four months follow-up after vaccination and generally do not assess how the current level of antibody correlates with an instantaneous risk of COVID-19. Another limitation in looking at serological correlates is the availability of approved quantitative binding essays with results that are traceable to certify WHO's national standard reference materials is limited. Next slide, please.

So, in summary, currently available commercial serology assays for SARS-CoV-2 are not authorized nor recommended for assessing protective immunity in natural infections or after vaccination. If ordering or reviewing serology results, please note that a positive test for spike proteins could indicate prior infection and/or vaccination. To evaluate for evidence of prior infection in an individual with a history of COVID-19 vaccination, an assay that specifically evaluates antibody to the nucleocapsid protein should be used.

These two points are noted on CDC COVID websites. Binding and neutralization antibody results after vaccinations have been reported from clinical trials and research studies. Adaptive immune responses to COVID-19 vaccination are sub-optimal in immunocompromised people, and variabilities noted based on severity of underlying immunocompromised and therapy. Data on serological correlates of protection are now being reported. Population thresholds are pending for binding and neutralizing antibodies. Interpretation and extrapolation to immunocompromised people will be challenging. Next slide, please.

This slide provides an overview of the adaptive humoral immune response. I won't go through it in detail, but just to show that there's a complex machinery that takes in the antigen, processes it, presents it to helper T cells. Those helper T cells then stimulate B cells, and those B cells mature to become plasma cells and secrete antibodies. And a subset of those B cells also become memory. So, it's a complex adaptive immune system shown on the left for the humoral side and for the right on the cellular side. Thank you again for the opportunity, and I'd like to hand it over to Dr. Farley. Thank you. Thanks. This is John Farley. Next slide, please. Next slide.

Good afternoon, everyone. And I appreciate the invitation to be here. I'm going to provide a brief overview of FDA's emergency use authorization of REGEN-COV, which is the trade name for casirivimab and imdevimab to monoclonal antibodies administered together. Those authorizations are for the treatment and post-exposure prophylaxis of COVID-19. As previously noted, these are not FDA approved. This is not an FDA-approved drug product but an authorized product under emergency use. Next slide, please.

So casirivimab and imdevimab are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2. The original authorization was for treatment, and that was in November of 2020 for the treatment of mild to moderate COVID-19 in adult and pediatric patients 12 years of age and older weighing at least 40 kg, with positive results of direct SARS-CoV-2 viral testing, who are at high risk for progression to severe COVID-19, including hospitalization or death. And for that progression risk, I would refer you to our fact sheets. And you'll note that we have allowed a fair amount of physician judgment in that determination. Currently, there's a limitation of authorized use for these products in the hospitalized patient setting, or in patients who have an oxygen requirement related to COVID-19. Next slide, please.

The authorized dose for treatment is 600 milligrams of casirivimab at 600 milligrams of imdevimab administered together as either a single intravenous infusion or by subcutaneous injection as soon as possible after a positive SARS-CoV-2 viral testing and within 10 days of symptom onset. For the treatment authorization, we strongly recommend intravenous infusion over subcutaneous injection, mainly because the achieving exposure above target will not be immediate with a subcutaneous injection. But it does remain a useful alternative route of administration when IV infusion is not possible, not feasible and would lead to a delay in treatment. What I point out to you is the link at the bottom where you can access our emergency use authorization page. You can scroll down to the casirivimab and imdevimab section, you can find the FDA fact sheets. You can also find the reviews, which have been shared publicly, that supported the authorization. Next slide, please.

So post-exposure prophylaxis was authorized on July 30, 2021. That is a rather complex authorization statement, so I want to go over it carefully. So, authorized in adult and pediatric individuals 12 years of age and older weighing at least 40 kg for post-exposure prophylaxis of COVID-19 in individuals at high risk for progression to severe COVID-19, including hospitalization or death. So, again, a high-risk determination is necessary first. Then those individuals should either be not fully vaccinated or not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination.

We provided some examples, individuals with immunocompromising conditions, including those taking immunosuppressive medications. And on the fact sheet there's a reference to CDC web pages that provide additional information. In addition, those individuals should have been exposed when individually infected with SARS-CoV-2 consistent with the close contact criteria per CDC that's printed on the next page in a footnote or who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting. Next slide, please.

There is a limitation of authorized use for the post-exposure prophylaxis authorization, that post-exposure prophylaxis with REGEN-COV is not a substitute for vaccination against COVID-19 and that REGEN-COV is not authorized at this time for pre-exposure prophylaxis for prevention of COVID-19. Next slide, please.

So, the authorized dose for post-exposure use is 600 milligrams of casirivimab and 600 milligrams of imdevimab administered together as either a single intravenous infusion or by

subcutaneous injection as soon as possible following exposure to SARS-CoV-2. There's -- either method of administration is acceptable. We do recognize -- we did recognize that particularly institutional outbreaks tend to go on for some time, and for individuals in whom repeat dosing is determined to be appropriate for ongoing exposure to SARS-CoV-2, for longer than four weeks and not expected to mount an adequate immune response to complete vaccination. The initial dose is 600 milligrams of casirivimab and 600 milligrams of imdevimab followed by subsequent repeat dosing of 300 milligrams of casirivimab and 300 milligrams of imdevimab administered once every four weeks for the duration of ongoing exposure. Next slide, please.

So, the data that supported this authorization, were the COV-2069 trial which Raj is going to go over. There's was a randomized double-blind placebo-controlled Phase 3 clinical trial studying the product for post-exposure prophylaxis of COVID-19 in household contacts of individuals infected with SARS-CoV-2. There was also a trial in healthy volunteers, a randomized double-blind placebo-controlled Phase 1 trial evaluating safety PK and immunogenicity of repeated doses of 600 milligrams of casirivimab and 600 milligrams of imdevimab administered subcutaneously. Again, this was in healthy subjects. Next slide, please.

So, in terms of uses which are not currently authorized, certainly for pre-exposure prophylaxis, there are a number of uncertainties. The heterogeneous group of patients, which patients are unlikely to mount adequate immune response to complete SARS-CoV-2 vaccination and what is or are the most appropriate intervention or interventions for which patients. In the hospitalized setting, we also have challenges with how to consider the data concerning seronegativity at baseline, which Raj will go over. There are ongoing and completed clinical trials that I expect to be informative. An example is a Phase 3 double-blind placebo-controlled study of an AstraZeneca monoclonal antibody product, which is being studied for pre-exposure prophylaxis of COVID-19 in adults. That's called the PROVENT study, and that has a listed actual primary completion date of May 5, so we would expect data soon.

I note that some physicians are requesting use of REGEN-COV under expanded access for users that are not presently authorized under EUA. So, the expanded access criteria need to be met, and the sponsor must agree to provide drug in those cases. Next slide, please.

I've included just for your reference the EUA statutory criteria, which you'll note is different than drug approval. And then next slide.

In addition, for your reference, I've included the expanded access criteria in the regulations, particularly those for individual patient use. I'll stop here and invite Colin, my colleague from CDC working at ASPR to talk about distribution and administration of monoclonal antibodies. Thanks, and next slide.

Good afternoon. I'm Colin Shepard, presenting on behalf of the Assistant Secretary for Preparedness and Response or ASPR. I appreciate this opportunity to give a brief overview of ASPR's role in the distribution and administration of monoclonal antibodies. Next slide, please.

So, this slide has a schematic showing the range of manifestations of COVID disease organized from left to right by clinical severity, along with the names of therapeutics underneath that had

been granted either FDA approval or an emergency use authorization. I'll be focusing on the left half of this slide, which shows the therapeutics intended for patients with mild to moderate COVID illness and given in order to prevent progression to severe COVID and reduce hospitalizations and also more recently, as you heard in the last talk, as post-exposure prophylaxis. The federal government has purchased a large supply of both casirivimab/imdevimab and bamlanivimab/etesevimab. And ASPR is responsible for the allocation and distribution of these therapeutics. Next slide, please.

So, our goal at ASPR is to facilitate the effective use of monoclonal antibody therapeutics to reduce COVID-19 hospitalizations in severe COVID. There are three monoclonal antibodies that have been granted emergency use authorizations for this purpose that you can see listed on the right side of this slide. The federal government has purchased the first two listed, REGEN-COV the first one there, casirivimab/imdevimab is currently available for order at no cost. Bam/ete distribution has been paused since June the 25th. And this is due to concern about resistance to this agent because of the beta and gamma variants that were prevalent in circulation in the US at that time. This pause is being continually reconsidered, especially now in light of the Delta variant being the dominant variant circulating. In fact, the bam/ete is expected to be active against the Delta variant. Sotrovimab, the third agent listed, has not been purchased by the government but is commercially available and expected to be active against the Delta variant. Next slide, please.

So, healthcare providers should know that they can order product, and right now that's REGEN-COV, directly from the sole distributor AmerisourceBergen. And there's information on ordering that can be found at phe. gov. There's an ample supply. Delivery is usually made in 48 hours or less. CMS reimbursement rates for the administration of these medications were increased a few months ago. They're now $450 for most outpatient settings and $750 for home administration. And there's additional information available on reimbursement and ordering at the websites, you know, provided on this slide. And I'll just conclude by, you know, reiterating that ASPR is committed to facilitating use of COVID therapeutics to reduce severe disease and hospitalization. There's an ample supply. And we have a clinical team that's glad to advise providers in how to get started using them to prevent severe COVID in their patients. We have a number of resources on our website, as well as weekly webinars for those interested in learning more and a dedicated email box where you can put forward your questions. So, we look forward to working with you, and we're -- we've been very pleased with the partnership thus far. So, with that, I'll thank you for your attention and turn it over to our next speaker, Dr. Gandhi.

Thank you very much. My name is Raj Gandhi. I'm an infectious diseases physician at Massachusetts General Hospital and a Professor of Medicine at Harvard University. It's a real pleasure to be here today speaking on this topic. I've been asked to review the evidence behind anti-SARS-CoV-2 monoclonal antibodies for treatment and prevention. So, we'll go through that evidence, and then we'll reflect upon its utility in immunocompromised patients. Next slide, please.

So, here's the rationale for anti-SARS-CoV-2 monoclonal antibodies for treatment. We know from observational data that delayed production of neutralizing antibodies correlates with fatal COVID-19. You can see in the graphic on your right that those individuals who are able to

mount a neutralizing antibody response early have a lower mortality than those who do not. And that has led to the question of whether providing passive immunity through antibody therapy will improve clinical outcomes. And the data I'll show you now emphatically shows that the answer is yes. And the reason why this is important for immunocompromised patients is we know that they tend to have a more difficult time mounting a strong antibody response. Next slide, please.

So, this is a schematic of outpatient treatment across the COVID-19 spectrum, starting with asymptomatic or pre-symptomatic infection, which is a positive test but no symptoms. Mild illness, of course, is mild symptoms without dyspnea. Moderate illness is having a preserved oxygen saturation but evidence of lower respiratory tract disease. Severe illness is when a person is hypoxic, and this is when typically people are in the hospital. They have extensive lung infiltrates. And then, of course, critical illness is respiratory failure, etc. The reason why this is important is we think the viral replication peaks right before people develop mild illness just as their transitioning into that phase and then begins to decline over time and so that, by the time people are severely ill, there's much less viral replication. Of course, inflammation seems to be driving a lot of the disease pathogenesis between the transition to moderate to severe illness and really persistent to clinical illness. So, the potential therapy, next slide, is really what we're focusing on is that early phase, which is the mild to moderate disease when there's a lot of viral replication, where antiviral therapy of which antibody therapy is an example is thought to be most effective. Next slide.

So, you've seen this authorization already. I won't belabor this. This is the authorization for several of the antibody products for treatment and as we just heard, bamlanivimab/etesevimab distribution is currently paused. So, this is for treatment. And then the next slide just reiterates the same information that Dr. Farley presented, which is the very recent issuance of an expansion of the emergency use authorization now to include post-exposure prophylaxis, and we've heard that discussed in terms of what that consists of in detail already. Next slide.

Okay. So now I'd like to go through first the data for the use of these antibodies for treatment. Next slide.

So, let's start with bamlanivimab/etesevimab for outpatient treatment. This is a Phase 3 clinical trial recently published in the New England Journal of Medicine. This looked at outpatients with mild to moderate COVID-19. Importantly, they were enrolled within three days of the first positive test, so they were enrolled really quite early. They all have one or more risk factors for developing severe COVID-19. A little over 1000 people in this study, they received the dose of bamlanivimab/etesevimab shown here, which is the 2800/2800 milligram dose. And what you see on the graphic on the right is time to hospitalization. There's a clear divergence between the antibodies group and the placebo group. And, overall, there was a 70% reduction in COVID-19 hospitalization or any cause of death by day 29 so a highly statistically significant benefit. The authorized dose, if you're really focused on the dose, is the 700/1400 milligram dose, and there are separate data supporting the use of that authorized dose that the FDA has put forward. Let's go to the next slide, please.

Here are the data for casirivimab/imdevimab for outpatient treatment. This is currently available as a pre-prep. Over 4000 individuals were in these trials, outpatients all with mild to moderate

COVID-19. They were randomized to receive placebo or intravenous casirivimab/imdevimab at various doses. The analysis that was done looked at those individuals who are PCR positive and had one or more risk factors for severe COVID-19. You can see the results in the graph on your right. The rate of hospitalization was 3. 2% or I should say hospitalization or any cause death was 3. 2% in the placebo group. It was 1% in the antibodies group. So that corresponds to a 70% reduction in COVID-19 hospitalizations or death in the 600/600 milligram group with this particular antibody. There was also more rapid resolution in symptoms in the individuals who received antibodies, a median of 10 versus 14 days in the group that received placebo. Next slide, please.

And then, lastly, sotrovimab, this is a single antibody, but this particular antibody is quite broadly active, at least in laboratory studies. So, this was studied also for outpatients with mild to moderate COVID-19 at high risk for hospitalization, just over 580 individuals randomized to receive intravenous sorovimab or placebo. You can see the results in the table; three -- 1% in the sorovimab group ended up in the hospital or died. And in the placebo group, it was 7%. And so that corresponds to an 85% reduction in hospitalization or death. Next slide, please.

So, Dr. Shepard just touched briefly on variants. In the next slide, I'll summarize what we know about variants based on in vitro studies. So, the Alpha variant, the B. 1. 1. 7, is susceptible to the authorized antibodies. The reason why bamlanivimab/etesevimab distribution was stopped was not because of Delta, and this is important. It was stopped because of Beta and Gamma, the B. 1. 351 originally isolated in South Africa, and the P. 1 originally isolated in South America. The Beta and Gamma have markedly reduced susceptibilities to bamlanivimab/etesevimab, and that's why the distribution was paused. Casirivimab/imdevimab and sotrovimab are expected based on laboratory data to retain activity. What about Delta? Dr. Shepard touched on this. Delta has markedly reduced susceptibility to bamlanivimab but a more modest reduction when the combination of bamlanivimab/etesevimab is studied in vitro. For Delta, the variant that we're most worried about right now based on its very high prevalence in the United States, Casirivimab/imdevimab and sotrovimab are expected to have activity. One point to make here is that what I've just shown you on this slide is in-vitro or laboratory susceptibilities. And we don't know enough yet about the clinical impact of these in-vitro susceptibilities. But I think, based on what we know, the current landscape is correct. So, let's go on to the next slide.

So, this shows you -- and go ahead and advance the slide and go back. So, this shows you the current NIH COVID-19 Treatment Guidelines. I should have mentioned at the outset that I'm a member of the COVID-19 Treatment Guidelines Panel, as well as the Infectious Diseases Society of America Treatment Guidelines Panel. So, based on the data as well as on the variants that we were just talking about, these monoclonal antibodies are recommended for outpatients with mild to moderate COVID-19 who are at high risk for disease progression. And that's as defined by EUA criteria. And the ones that are recommended by the NIH and IDSA are casirivimab plus imdevimab or sotrovimab. And for the reasons I mentioned, the variants currently, currently we recommend against the use of bamlanivimab plus etesevimab, largely based on the variant information that we just talked about. Let's go on to the next slide, please.

So, this is one of the questions that I see appearing in the chat. It's a question that we ask ourselves every day. It's very important to acknowledge that the data that I've shown you thus far

largely was derived from participants prior to vaccination. So, we don't yet have strong data on the role of these monoclonal antibodies in people who have breakthrough infection after vaccination or people who are partially immunized or, as I'll show you near the end, immunosuppressed patients.

Nevertheless, the NIH and the CDC currently recommend that, for people who develop COVID-19 after receiving vaccination, prior vaccination should not affect treatment decisions, including the use of and timing of treatment of monoclonal antibodies. And the reason for that is -- the reasoning is that if one has a post-vaccination infection, that one is shown that their immune system is not yet strong enough to contain the virus and, therefore, these antibodies are still considered appropriate for use. But this is an area that, of course, it would be good to have more data on. But the data I've shown you is largely from unvaccinated people. But this is the current recommendation. And let's go on to the next slide.

So now let's shift from treatment to post-exposure prophylaxis. And one thing that those of us who've done infectious disease for some time know is there are a number of antibodies that we use for post-exposure prophylaxis, hepatitis B immunoglobulin, rabies immunoglobulin, varicella zoster immunoglobulin.

So, there's a long history of using immunoglobulins or antibodies for post-exposure prophylaxis. But now let's look at what are the data for anti-SARS-CoV-2 antibodies for post-exposure prophylaxis. Next slide.

So, the first studies I want to mention is the bamlanivimab post-exposure prophylaxis study that was done in long-term care facilities. This is a Phase 3 clinical trials done among residents and staff of long-term care facilities. Those facilities have at least one COVID-19 case. There were a little over 1178 participants that were randomized to get the antibody or placebo. And you can see in the graphic on the right the main results. Among residents in the prevention population, the incidence of mild or worse COVID-19 was 80% lower in the bamlanivimab group. And this was, of course, statistically significant. Those residents who became infected were also more likely to have low viral loads and to clear the virus more quickly. So this is one bit of evidence that I believe informed the FDA as they made their determinations for EUA. Let's go to the next slide.

These are I think the most important data, though, what -- that led to the expansion of the EUA. This is post-exposure prophylaxis with casirivimab/imdevimab published in the New England Journal just in the last week or two. Phase 3 placebo controlled trial among household contacts of a person who has a positive SARS-CoV-2 test within the past 96 hours. Casirivimab/imdevimab at the dose shown here, 600/600 or placebo was given subcutaneously. So this is in difference -- this is a difference than from the treatment trials. This is given subcutaneously. You can see that among those participants who are PCR negative and seronegative at baseline, this was about 1500 individuals, there was an 81% reduction in symptomatic SARS-CoV-2 infection in the casirivimab/imdevimab group, and this was highly statistically significant. In the table you see the proportions; 7. 8% in the placebo group develop symptomatic disease, 1. 5% in the antibiotic group. That corresponds to the 80 -- 81% reduction. Among infected participants, the antibody group had a shorter duration of symptoms. There's a

typo on the slide. This should be 1. 2 versus 3. 2 weeks, not days. And so there was a statistically significant shorter duration of symptoms. And there was also a shorter duration of high viral loads shown here.

The next slide shows you just schematically the separation between the placebo group and the casirivimab/imdevimab group, the placebo in the blue, the antibodies in the red. And you can see really quite a rapid divergence over time for post-exposure prophylaxis. Let's go to the next slide.

So, the last topic I'm going to discuss briefly, very briefly before we talk about immunocompromised patients for a moment is patients who are hospitalized due to COVID-19. Everything I've shown you thus far are on outpatients. Everything I've shown you thus far is on pre -- on post-exposure prophylaxis. What about what happens to someone who gets sick enough to be in the hospital? Let's go to the next slide.

So now we're all the way over to the right of this schematic that I showed before. We're talking largely about people with severe disease and critical disease. Now, recall this is when we think viral replication is diminishing. This is where we know dexamethasone and some of the immunomodulators have an important role. But what can we say about antibodies in people who have severe or critical disease? Next slide.

So, there's a number of studies that have been looking at monoclonal antibodies in hospitalized patients, and a lot of these data have come out of the ACTIV-3 NIH-sponsored trial. The first of these data came from a study of bamlanivimab monotherapy published in the New England Journal, that -- when you look at the overall results in hospitalized patients with bamlanivimab monotherapy, there was not a benefit in hospitalized patients with COVID-19. Now, very recently, there's a preprint that looked at a sub-analysis of this important study. And this sub-analysis found that a subset of those individuals who were hospitalized with COVID-19 who did not have neutralizing antibodies and who have elevated viral markers, that that subset appeared to benefit. And that's quite interesting, especially in light of the data that I'll show you in a moment from the recovery trial.

A second trial of casirivimab/imdevimab in hospitalized patients on high-flow oxygen mechanical ventilation was stopped. Also, in ACTIV-3, the drugs -- the antibodies sotrovimab and a combination of two antibodies from BRII also were stopped in ACTIV-3. And then, finally, at least as far as I'm aware, there is an AstraZeneca vaccine that's being -- continued to be studied as part of ACTIV-3. So here are some, I guess, I would say mixed data on antibodies for hospitalized patients. But the data that I think is the most provocative is that on the next slide.

So, I think all of us are aware of the recovery study. This is a study being done in the United Kingdom. In this particular study, the focus was on the use of casirivimab/imdevimab in hospitalized patients. A large number of individuals, over 9000 individuals who were hospitalized were randomized to receive usual care with casirivimab/imdevimab or usual care alone. And the dose of antibody given in this hospitalized patient study was 4000 milligrams of each of the two antibodies. This is substantially higher than the outpatient treatment doses or the post-exposure prophylaxis doses that we've been discussing.

But what were the results? If you look overall, if you looked at all comers, there was no difference in 28-day all-cause mortality between the group that got casirivimab/imdevimab and the group that got placebo. So, if you looked at all comers, no different. But this is the important part. If you'd looked at the seronegative group, the people who were seronegative for anti-spike protein antibody, now you see a reduction in mortality with casirivimab/imdevimab. So take your eyes over to the right-hand side, the top two curves are usual care versus the antibodies. And you can see really a quite a marked divergence in mortality in the seronegative group in particular. And that difference is 24% mortality versus 30% mortality for a rate ratio of 0. 8 so 20% reduction. If you look at the seropositives, you see no benefit of the antibodies at all. Let's go to the next slide. So-caution.

This is rapidly evolving information with more to come. Casirivimab/imdevimab as of the 12th of August 2021 is not yet authorized for treatment for hospitalized patients. We very much need a rapid and reliable serology test to identify those individuals who are seronegative, those individuals who might benefit. And as of this moment, casirivimab/imdevimab is only available through expanded access programs for hospitalized patients who are not on high-flow oxygen or who are mechanically ventilated. Let's go to the next slide.

So, in the last few minutes, I'll bring this back to immunocompromised people. I started out this talk talking about the fact that immunocompromised people are slower to generate antibody responses. And the data that I just showed you from recovery is focused showing benefit in hospitalized patients in people who don't have an antibody response. So, let's go to the next slide.

So, an important point here is all of the data have shown you from both treatment trials as well as prevention trials have a relatively small proportion of immunocompromised patients in the bam/ete Phase 3 trial that we started off with, about 6 1/2% of those individuals were immunocompromised. In the casirivimab/imdevimab Phase 3 treatment trials, it's about 3%. So very small numbers or small proportion, certainly. In the long-term care facility study with bamlanivimab, it's a higher proportion. It's about 19% of the prevention cohort. But -- and this is now when we get into the theoretical rationale.

We do know that immunocompromised patients who may not mount an endogenous antibody response may have protracted viral replication. My colleague John Lee, Dr. John Lee at Brigham Women's Hospital published the case of a person who had replication that went on for close to 140 days or so, a very highly immunocompromised individual. There's also the theoretic and actually observed point that these monoclonal antibodies may be particularly effective at reducing viral load in patients who don't mount their own antibody response. Let's see the next slide.

So, this is from one of the treatment trials looking at the casirivimab/imdevimab combination. If you look at the left, you see people who entered who were antibody negative. And the top line is placebo, and the bottom two lines are the two different doses of the antibodies. And you see a divergence in viral replication, a reduction of what the antibodies. And then the people who have their own endogenous antibody response less of a splay. Let's go to the next slide.

I think this is an older version of the slide set, so I apologize for the animations there. But this is just the summation of what you've already heard, which is the authorizations for treatment for high-risk patients. The particular focus on casirivimab/imdevimab and sotrovimab. You've already heard Dr. Farley talk about the fact that these antibodies aren't authorized for use in people who are hospitalized due to COVID-19 but may be used in people who are hospitalized for reasons other than COVID-19. And then we've already reviewed the fact that, in the future, we need a rapid and reliable serologic test to tell us who might benefit among the hospitalized patients and to, again, reiterate these are not yet authorized for hospitalized patients who are admitted due to COVID-19. And then the post-exposure prophylaxis finding I think is a very important one.

So, the last slide is where I'll conclude, and then we'll open it up for what I hope to be a robust discussion. This is really just a summation of everything you've heard so far. The authorization of casirivimab/imdevimab for post-exposure prophylaxis the -- similarly the use of these antibodies for high-risk outpatients with mild to moderate disease. And then once we get into severe disease, we're aware of the data for dexamethasone in some patients, other than [Cross-talk] With that, I will conclude.

Excuse me. Can we please mute our phones if you're not presenting.

With that, I will conclude and look forward to the discussion.

Thank you, Dr. Gandhi.

Presenters, thank you so much for providing our audience with this timely information. We will now go into our Q&A session. Please remember to ask your question using Zoom. Click the Q&A button at the bottom of your screen; then type your question. Do please note that we receive many more questions than we can answer during our webinars.

So, our first question to our presenters -- and just a note to our presenters, since we have multiple presenters, please, if you don't mind, identifying yourself when you answer the question. That's much appreciated. Our first question is for immunocompromised persons who have been vaccinated and have been recently exposed to SARS-CoV-2, how do you suggest determining whether they should be considered for post-exposure prophylaxis with REGEN-COV product? Is there a role for antibody testing here?

I could start by saying that the emergency use authorization does not call for antibody testing as part of their authorization, and Dr. Farley should speak to that in more detail. I think right now it's based on the fact that if you have an immunocompromised individual and you're concerned that they may not have developed their own antibody response, then you base it on whether they've had a exposure as Dr. Farley said, as defined by the CDC. But, Dr. Farley, do you want to comment on the role of antibody testing to help decide about post-exposure prophylaxis?

Yeah. Thanks, Dr. Gandhi. I just don't think we have any data that would be informative at this point so that we left it up to physician judgment in the authorization. One thing I will say is that it's important to make a decision early, and one of the things that an antibody test would do is it

would certainly delay the initiation. At least where I am, it takes some time to get these results back. And then, as was just said, we don't have the validated information that we really need, And I think that's a very important topic for future research is a validated test to predict who would benefit most.

Thank you very much for that. Next question asks, based on your presentation, can you please elaborate or reiterate the preference for IV over sub q administration?

This is John Farley. I'm happy to take that. So that was particular to the treatment use when you had a sick patient in front of you. And certainly with sub q administration, the exposure, the immediate exposure is not as high. And, in fact, there have been modeling -- there's been modeling of, you know, when is the target achieved. It certainly is fairly soon, sometime in the first 6 to 24 hours. But if it's a sick patient, we felt that it was reasonable to list intravenous administration as the preferred mode of administration.

Thank you very much for that. Next question asks, for those severely immunocompromised persons, when should we consider administering high-dose 8 gram REGIN-COV product available to compassionate use rather than the 1. 2 gram dose currently authorized by the EUA, either for early treatment or post-exposure prophylaxis? And do you think the higher dose will be authorized by the Food and Drug Administration?

I'll start. Based on the data that we've seen, I think the authorized dose is the dose that should be used. We didn't get into all of this because of the interest of time, but I think the data in support of the authorized dose, even in immunocompromised patients, is strong. So, I don't know that the larger dose that was used in the [inaudible] trial is needed even for immunocompromised patients. But I'm happy to hear Dr. Farley's thoughts as well.

You know, I agree. For the two authorized uses, the dose in the authorization is based on good data; and I don't think that a higher dose is needed.

Thank you very much. And in the remaining time, I'd like to compile two of our questions into one which we've seen in the Q&A box a bit. And that is, a, is there a certain age group? And I'm assuming they mean an older. Is there an age group that would be considered immunocompromised specifically based on their -- that criteria, the age criteria? That's one. And, two, can you also speak about the use of the monoclonal antibodies in patients under 18 years of age.

I'm going to let Dr. Farley go first. Yeah. So, this is John. I -- certainly for this second one, in terms of pediatric use, it is authorized down to 12 years of age and older, providing the patient weighs at least 40 kilograms. We are certainly working at the FDA and with companies on looking at use in younger children, and certainly would consider that under expanded access at this point. I don't have data in terms of the geriatric population and what a threshold would be to consider immunosuppression. I don't know if you do, Dr. Gandhi. What I'll say, certainly, we've been impressed by the vaccine responses in older individuals turning out to be quite, quite good when you look at least the first six months or so of the vaccine data. And so, even though I think a lot of us prior to the vaccine authorizations worried about our older patients in terms of their

immune response, the vaccines have done well. Now, so I guess I've worried currently more about my immunocompromised patients where, of course, we all know that the vaccines, you know, the antibody response, at least, is not as robust as in immunocompetent individuals. Now, it's a very complicated topic. I'm looking forward to ACIP's discussion tomorrow on this immunocompromised. But I think I've been pleasantly surprised that our older patients have done well in large part, not entirely but in large part with the vaccines. And so that would be my comment about older individuals so --.

Thank you very much for that. And, with that, I want to take a moment to thank everyone for joining us today with a special thanks to our presenters, Dr. Raizes, Dr. Gundlapalli, Dr. Farley, Dr. Shepard, and Dr. Gandhi. Thank you so much for sharing such timely information in your expertise with our audience.

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