Good afternoon. I'm Commander Ibad Kahn, 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 would like to welcome you to today's COCA call, What Clinicians Need to Know About the New Oral Antiviral Medications for COVID-19. All participants joining us today are in listen only mode. Continuing education is not offered for this COCA call.

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. The video recording of this COCA call will be posted on COCA's webpage and available to view on demand a few hours after the call ends. If you're a patient, please refer your questions to your healthcare provider.

For those who may have media questions, please contact CDC Media Relations 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 are pleased to have with us Captain Lauri Hicks. Captain Hicks is currently serving as the Chief Medical Officer for CDC's COVID-19 response.

Captain Hicks also service as the Division Director for the Division of Healthcare Quality Promotion in CDC's Office of Antibiotic Stewardship. Dr. Colin Shepard. Dr. Shepard is CDC's liaison to the Assistant Secretary for Preparedness and Response, ASPR.

Dr. Stephanie Troy. Dr. Troy is a Senior Medical Advisor in the Division of Antivirals at the Food and Drug Administration, FDA. Dr.

Aimee Hodowanec. Dr. Hodowanec is a Senior Medical Advisor in the Division of Antivirals at the Food and Drug Administration, the FDA. And Dr. Alice K Pau.

Dr. Pau service as the Executive Secretary on the NIH COVID-19 Treatment Guidelines Panel, and is also a clinical pharmacy specialist at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, the NIH. It is now my pleasure to turn it over to Captain Hicks. Captain Hicks, please proceed.

So I'm delighted to have this opportunity to provide an update on the Omicron variant and what we're learning with you.

Next slide, please. Next slide. There are answers to several questions we're closely tracking at CDC, including how transmissible is the Omicron variant? How severe is Omicron compared to Delta and other variants? How well do vaccines and prior infection protect against infection, transmission, and death due to Omicron? And then lastly, and the focus of our session today, what therapeutics are available to treat Omicron infections?

Next slide. We'll start with some data on Omicron transmission.

Next slide. Oh, I'm sorry, stay with this slide! There are an unusually large number of mutations across the Omicron SARS-CoV-2 genome. 15 of which are within the receptor binding domain,

which allow Omicron to be more infectious and transmissible than the Delta variant and resist neutralization by vaccine and infection induced antibodies. And so, what does this mean? People who have been previously infected, even with a Delta variant, or ancestral strains, do not necessarily have protection against infection with Omicron.

Next slide. I recognize that this is not likely news to most of you, but US COVID-19 cases have rapidly increased since the first US Omicron case was reported on December 1st, 2021. Case counts are now exceeding peaks from last winter, and the current seven day daily average of cases is about 751,000 cases per day, an increase of about 47% compared to the previous week.

Next slide. Data suggests that the Omicron variant is associated with higher transmissibility. And I'm show you here a Danish household study that looks at secondary attack rates.

What we learned is that the attack rates were similarly high for both Omicron and Delta infections in unvaccinated persons. However, when we look at fully vaccinated and boosted individuals, both fully vaccinated and boosted individuals have a markedly higher secondary attack rate comparing Omicron to Delta. But it's important to note that boosted individuals have the lowest attack rates for both variants.

Next slide. So I want to briefly comment on what we're learning about severity of illness.

Next slide. This slide shows you that US hospitalizations are surpassing the peaks in hospitalizations that we experienced last winter. The seven day average of hospital admissions is about 19,800 per day. An increase of about 33% over the previous week. And the seven day average daily deaths are about 1,600 per day, which is an increase of about 40% over the previous week.

We continue to learn more about Omicron each and every day, including about the severity of disease caused by this variant. And just yesterday, a pre-print study of data from Kaiser Permanente Southern California provided some insight into clinical outcomes among patients infected with Omicron. This is a study that leverages mathematical modeling to estimate risk of hospitalization and severe disease from a healthcare system that provides care to a very large portion of the population in California, 19% of the state's total population. And they noted substantially reduced risk of severe clinical outcomes in patients were infected with the Omicron variant compared with Delta.

Next slide. We must also understand how well our vaccines are working to understand what policies will make the most sense to protect the population from the Omicron variant.

Next slide. And this slide is a summary of the ability of sera from persons with different vaccine and infection scenarios to neutralize the Omicron variant. And it compares Omicron neutralization to ancestral and Delta strains. For most individuals who have not been previously infected, but have received two doses of mRNA or one dose of the Janssen or Johnson and Johnson vaccine, neutralization is below the limit of detection.

And is 11 to 127 times lower for Omicron compared to Delta and ancestral strains. Neutralization is above the limit of detection in many vaccinated people who received a booster or among those who were previously infected and vaccinated. But I want to really mention that neutralization is still quite a bit lower for Omicron compared to Delta and ancestral strains.

Next slide. Data from the UK show that Pfizer mRNA vaccine effectiveness, or VE, is lower for infections due to Omicron compared to Delta.

And on this slide, you see black squares, which represent VE for Delta, and the gray circles represent the VE for Omicron. You can see that in every instance on this figure, Omicron VE is lower than for Delta and the difference is particularly marked for individuals who are several weeks out from their primary series. So that is shown on the left hand side of the slide. And then in the middle and the right hand side of the slide, you can see boosting with either the Pfizer in the middle or in Moderna mRNA vaccines. Now boosting with either of these mRNA vaccines does lead to better protection against infection, but we do see some waning, I think that's important to note.

Notably, emerging data suggests that vaccinated persons and particularly those who are boosted remain well protected against hospitalization and severe disease.

Next slide. I will finish up my presentation with one slide on the Omicron variant and monoclonal antibody therapies.

Next slide. Data show that susceptibility to monoclonal antibody therapies appears to be lower for the Omicron variant compared to Delta, with the exception of Sotrovimab.

And that's what this slide is showing you here. And at the end of the day, when we're looking at all of these different options, Sotrovimab is the only monoclonal antibody option that is recommended for treatment of individuals infected with the Omicron variant at this time. Sotrovimab is available through an emergency use authorization for non-hospitalized patients with mild to moderate COVID-19, who have certain risk factors for severe disease. And I want to acknowledge that both-- I would say availability, a requirement for intravenous administration, and the need to administer early in the course of illness to create some logistical challenges. We also know that there are several other monoclonal antibody options in the pipeline, and so this gives us hope and I will also say the hopeful news of this session is that we now have multiple new antiviral options.

Next slide. So in summary, accumulating evidence suggests that the Omicron variant is more transmissible, but causes less severe disease. Our currently authorized vaccines offer less protection against infection due to Omicron compared to ancestral strains and previous variants, but we're still seeing that they provide benefit. So it's important to increase uptake of both primary vaccination and boosters in all eligible populations to optimize protection. Especially against hospitalization and severe disease.

And lastly, susceptibility to monoclonal antibodies appears to be lower for Omicron compared to Delta. Sotrovimab is likely effective, and the antivirals which you will hear more about next

offer additional treatment options. So thank you very much, and I am going to pass the mic to Dr. Colin Shepard.

Good afternoon. Thank you. I'm Colin Shepard, I'm a medical officer assigned to the HHS COVID Therapeutics Team, and I'll be giving a very brief overview of the distribution of oral antivirals for COVID-19. Let me see the next slide, please. There we go.

Thank you. The federal government has been distributing therapeutics for COVID-19 since November 2020 as part of its overall pandemic response. And the Office of the Assistant Secretary for Preparedness and Response within HHS is the lead for distribution of COVID therapeutics and is committed to equitable and transparent distribution of these medications. So two oral antivirals that Dr. Hicks referenced and that you'll hear more about in the upcoming presentations, Paxlovid and Molnupiravir, have recently been granted emergency use authorizations by the FDA.

And the federal government has purchased the initial available supply. ASPR is distributing this supply using a state and territory coordinated system. And under this system, HHS determines the weekly amount of therapeutic product available to each state and territory. Then the health departments for the states and territories determine which sites in their jurisdictions receive product and how much. And then the sole distributor of these medications sends the product directly to the administration site according to the state territorial health department instructions.

So this distribution system was instituted four months ago, approximately. When demand for COVID therapeutics began to exceed available supply. And jurisdictional allocations are based on the formula that takes into account past seven day incidence COVID hospitalizations and case counts in that jurisdiction. So-- and HHS firmly believes this approach best serves the goal of equitable distribution as supplies of COVID therapeutics remain extremely limited and the federal government seeks to procure more therapeutics. This week, the federal government made available approximately 100,000 treatment courses of Paxlovid and 400,000 treatment courses of Molnupiravir.

Next slide, please. So recognizing that the current supply constrained environment poses a host of challenges to clinicians and clinical facilities, ASPR is making every effort to support the clinical community with resources to understand these new agents and to provide updates. This slide has links to our clinical implementation guide, which is a comprehensive resource for clinical staff implementing COVID therapeutic service, as well as our main therapeutics page, which has a lot of other resources.

Next slide, please. And then this slide has our schedule of stakeholder engagements that happen throughout the week.

These are webinars that anyone with equity in this process is invited to attend to learn more, ask questions of HHS staff, as well as representatives of the companies that produce these medications. Please also note the COVID-19 therapeutics at HHS. gov email address Which is where you can direct any specific questions that you may have. And with that, thank you for your attention, I'm going to turn it over to our next speaker.

Hi. This is Dr. Stephanie Troy from FDA.

Next slide, please. And thank you for inviting me to speak about the emergency use authorization for Paxlovid for COVID-19.

Next slide, please. So, this slide shows the content of what I'll be speaking about today. All the information I will be discussing is in the Paxlovid fact sheet and the Paxlovid EUA review. And links to those documents are included on my last slide.

Next slide, please.

So what is Paxlovid? Paxlovid is a combination product containing Nirmatrelvir co-administered with Ritonavir. Nirmatrelvir is a SARS-CoV-2 main protease inhibitor. It blocks the proteolytic cleavage of the polyprotein step in the SARS-CoV-2 replication cycle, as depicted by the red X in the figure. Ritonavir is a strong cytochrome P450 3A inhibitor, and it is included to increase Nirmatrelvir plasma levels. Ritonavir in higher doses was previously used as HIV protease inhibitor, but Ritonavir alone has no activity against SARS-CoV-2.

Next slide, please. So Paxlovid is dosed as two 150 milligram tablets of Nirmatrelvir with one 100 milligram tablet of Ritonavir orally twice a day for five days without regard to food and as soon as possible after COVID-19 diagnosis, and within five days of symptom onset. Each carton contains five blister packs, one for each day. And because dose reduction is needed for moderate renal impairment, each shipment of Paxlovid contains instructions for pharmacists on removing the excess Nirmatrelvir tablets when filling prescriptions that specify the moderate renal impairment dose, as well as affixing stickers to the blister packs and carton to cover the dose instructions with the dosing instructions for moderate renal impairment.

Next slide, please.

Paxlovid is authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40 kilograms with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Next slide, please. Paxlovid is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19. Now we deliberately worded this limitation in this way to allow for use in hospitalized patients in several scenarios. The first is depicted by the footnote.

And this is a situation where a patient is started on treatment with Paxlovid as an outpatient for mild to moderate COVID-19, and then worsens, and requires hospitalization due to severe or critical COVID-19, in which scenario they may complete the full five-day treatment course per the healthcare provider's discretion. A second scenario is if a patient has mild to moderate COVID-19 and is hospitalized either for an unrelated reason or because their provider would like them to have extra monitoring, for example for drug interactions. And in that scenario, they may initiate treatment in the hospital under this EUA. Paxlovid is also not authorized for use as pre-

exposure or post-exposure prophylaxis for prevention of COVID-19 or for use for longer than five consecutive days.

Next slide, please.

So the data on efficacy for Paxlovid comes from the critical trial of EPIC-HR. Which is a phase 2/3 double blind study in over 2,000 non-hospitalized, symptomatic adults with a laboratory-confirmed SARS-CoV-2 infection who were randomized 1:1 to receive Paxlovid or placebo for 5 days. The study population was enrolled within five days of symptom onset, had at least one risk factor for progression to severe disease, had no prior COVID-19 vaccine receipt, or prior COVID-19 infection, and were allowed to use standard of care treatment, which at the time was the authorized COVID-19 monoclonal antibodies. However, the primary analysis population was limited to subjects who did not receive the COVID-19 monoclonal antibodies and only about 6% of the total studied population received them. 98% of the SARS-CoV-2 variants identified in EPIC-HR were Delta.

Although there were no clinical data for Paxlovid against Omicron, because Omicron was not prevalent during the trial, preliminary biochemical and cell culture data indicate that Nirmatrelvir retains activity against the Omicron variant.

Next slide, please. This slide shows the efficacy data for the primary end point of COVID-19 related hospitalization or death from any cause through day 28. As you can see, 8, or 0. 8% of Paxlovid recipients, met the primary end point, versus 66 or 6.

3% of placebo recipients. Which translates an absolute risk reduction of 5. 6% and a relative risk reduction of 88% for the primary end point with Paxlovid. Which was highly statistically significant. You can also see that there were no deaths in the Paxlovid group compared to 12 deaths in the placebo group.

This treatment effect was generally consistent across subgroups, including baseline serology status. Meaning that patients who were sera positive at baseline, the likely to be hospitalized or die overall also had a positive treatment effect with Paxlovid.

Next slide, please. The only adverse events that were seen in at least 1% of Paxlovid recipients, and also had a higher frequency, meaning a five subject or greater difference versus placebo, were dysgeusia, which was generally described as metallic taste and the mouth. Diarrhea, hypertension, and myalgia.

Next slide, please. Paxlovid has a lot of drug interactions. Paxlovid is a CYP3A inhibitor and is also metabolized by CYP3A. This means that Paxlovid may increase plasma concentrations of medications metabolized by CYP3A, which could lead to clinically significant adverse reactions, including fatal events from greater exposures of concomitant medications. In addition, medications that inhabit or induce CYP3A may increase or decrease Paxlovid concentrations, leading to loss of therapeutic effect of Paxlovid and possible viral resistance from decreased Paxlovid exposures.

Next slide, please. As a healthcare provider, you should inform patients that Paxlovid may interact with some drugs and is contraindicated for use with some drugs. Obtain a complete medication list from your patient, including non-prescription drugs and herbals. Check for clinically significant drugs interactions, and I've included two links here to websites that can help you to do this. And based on the drug interactions, decide if Paxlovid use is appropriate versus an alternative authorized treatment.

And if appropriate, whether your patient should hold, change, or dose reduce other medications while taking Paxlovid, or if additional monitoring may be needed.

Next slide, please. Paxlovid needs a dose adjustment for moderate renal impairment, as shown in the table. And is not recommended for severe renal impairment, because the appropriate dose has not been determined. As a healthcare provider, you should determine the appropriate Paxlovid dose for your patient and whether Paxlovid can be given at all.

Specify the numeric dose of each active ingredient, Nirmatrelvir and Ritonavir in every Paxlovid prescription. Counsel patients with moderate renal impairment about renal dosing instructions. And inform them that the blister cards will be altered by the pharmacist to remove unneeded tablets.

Next slide, please. For other populations, no dosage adjustment is needed for mild or moderate hepatic impairment, but Paxlovid is not recommended for severe hepatic impairment due to lack of pharmacokinetic and safety data in this population.

There are no available clinical data on Paxlovid in pregnancy or with breastfeeding. In animal studies, reduced fetal body weights were seen at about tenfold higher Nirmatrelvir exposures than we'd expect in humans with the authorized dose, but no other adverse developmental effects were seen. There are no available clinical data for Paxlovid in children. However, the authorized adult dose is expected to result in comparable serum exposures in patients 12 of years of age and older and weighing at least 40 kilograms. So the authorization was extended to this population.

Next slide, please. So in summary, Paxlovid was authorized in December for the treatment of mild to moderate COVID-19 in adults and pediatric patients 12 years of age and older and weighing at least 40 kilograms, who are at high risk for progression to severe COVID-19. Paxlovid reduced COVID-19 related hospitalization and death by 88% when given within five days of symptom onset without concerning safety findings in the clinical trial, EPIC-HR. Key things to remember when prescribing are the multiple drug interactions, the reduced dose for moderate renal impairment, and that Paxlovid is not recommended with severe renal impairment or severe hepatic impairment.

Next slide, please.

And these are some helpful links that you can look up some of these resources and more information, and at this point, I'm going to pass the mic off to my wonderful colleague, Dr. Aimee Hodowanec.

Thank you very much, Dr. Troy.

Next slide, please. Good afternoon, everyone, my name is Aimee Hodowanec. And I'd like to thank the organizers of this call for giving me the opportunity to provide an overview for clinicians on the Molnupiravir EUA.

Next slide, please. So this is an outline of the content I will be presenting over the next 10 minutes. And as with Dr. Troy's presentation, nearly all of the information I will be providing can be found in the Molnupiravir fact sheet for healthcare providers. And additionally, I will be pointing out various ways to access the fact sheet throughout my presentation.

Next slide, please. So how does Molnupiravir work? Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis.

Next slide, please. Under EUA, Molnupiravir is authorized for the treatment of mild to moderate COVID-19 in adults 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 whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate.

Next slide, please.

There are several limitations to this authorized use, specifically, Molnupiravir is not authorized for use in patients less than 18 years of age, for initiation of treatment in patients requiring hospitalization due to COVID-19. And this is because benefit of treatment with Molnupiravir has not been observed in subjects when treatment was initiated after hospitalization for COVID-19. However, should a patient require hospitalization after starting treatment with Molnupiravir, the patient may complete the full five-day treatment course per the healthcare provider's discretion. Molnupiravir is also not authorized for use for longer than five consecutive days, or for pre- or post-exposure prophylaxis for prevention of COVID-19.

Next slide, please.

The authorized Molnupiravir dosage is 800 milligrams taken orally every 12 hours for five days with or without food. Molnupiravir comes in 200 milligram capsules, so patients need to take four capsules every 12 hours for five days. It should be taken as soon as possible after a diagnosis of COVID-19 has been made and within five days of symptom onset. Completion of the full five-day treatment course and continued isolation in accordance with public health recommendations are both important to maximize viral clearance and to minimize transmission of SARS-CoV-2. I've included on the right side here an image of the Molnupiravir container label, and wanted to point out here all of the containers will contain this QR code, which will take you to the Molnupiravir.com website, where providers and patients can access the healthcare provider fact sheet and the patient fact sheet for Molnupiravir.

Next slide, please. The data and support of the Molnupiravir EUA comes from trial P002, or the MOVe-OUT trial. This was a phase 2/3 randomized placebo controlled, double blind trial in non-

hospitalized adults with COVID-19. In the top of this slide, I show the part two or phase-- sorry, part one or phase two portion of the trial, which was a dose ranging study.

And then in the bottom, we depict the part two or phase three portion of this study, in which a planned total of 1550 participants were randomized one to one to receive either Molnupiravir or a placebo for five days. The primary endpoint in this trial was the percentage of participants who were hospitalized or died through day 29 due to any cause. And the data in support of the EUA specifically came from this part two or phase three portion of the trial.

Next slide, please. This is an outline of the key eligibility criteria for participation in trial P002.

Outpatient adults with mild or moderate COVID-19 were eligible for participation if they had laboratory confirmed SARS-CoV-2 infection with sample collection, as well as onset of COVID-19 symptoms, within five days prior to randomization. All participants in P002 were at increased risk for severe illness from COVID-19. The specific high-risk criteria, as outlined in the P002 protocol, are listed here. SARS-CoV-2 vaccination was prohibited. Pregnant individuals were excluded.

And contraception use was required.

Next slide, please. Here we present the efficacy results for the full randomized population of the phase three portion of trial P002. As previously noted, the primary endpoint for this trial was all cause hospitalization or death through day 29. This endpoint was met by 6.

8% of Molnupiravir participants compared to 9. 7% of placebo participants, for an adjusted risk difference of 3% and an adjusted relative risk reduction of 30%. In the bottom portion of this table here, you can see we also show the mortality component of the endpoint. There were nine deaths among placebo participants compared to one among Molnupiravir participants.

Next slide, please.

Molnupiravir was generally well tolerated in trial P002 participants. Here we display adverse reactions occurring in at least 1% of participants receiving Molnupiravir with adverse reactions being defined as adverse events attributable to study intervention per the investigator. There were three adverse reactions that met this threshold and those were diarrhea, nausea, and dizziness. And all three of these occurred at the same rate in the Molnupiravir and placebo groups.

Next slide, please.

So what do clinicians need to know when prescribing or considering prescribing Molnupiravir? Molnupiravir is not authorized for use in patients less than 18 years of age. And this is because data from animals show that Molnupiravir may affect bone and cartilage growth, which is of particular relevance to pediatric patients. Molnupiravir may be used regardless of COVID-19 vaccination status. Breastfeeding is not recommended during treatment with Molnupiravir and for four days after the final dose. No drug interactions have been identified based on the limited available data.

And no dosage adjustment is recommended in patients with any degree of renal or hepatic impairment.

Next slide, please. There are some specific unique considerations regarding Molnupiravir use in pregnancy. First and foremost, Molnupiravir is not recommended for use during pregnancy. Based on animal data, Molnupiravir may cause fetal harm when administered to pregnant individuals.

However, if a healthcare provider determines that the benefits of Molnupiravir outweigh the risks for an individual pregnant patient, they must first counsel the patient regarding these known and potential benefits and potential risks of Molnupiravir use during pregnancy. They must also document that the patient has been made aware of these known and potential benefits and potential risks of Molnupiravir. And lastly, they must make the individual aware of the existence of a Merck sponsored pregnancy surveillance program. And if the individual agrees to participate in this program and allows the prescribing healthcare provider to disclose their information to Merck, then the prescribing healthcare provider must provide the patient's name and contact information to Merck, either through the 1-800 number that we have listed here or electronically through the website that has been established.

Next slide, please.

These are some general prescriber requirements for Molnupiravir use under EUA. There are numerous requirements and to help make sure that prescribers are aware of these and can find these easily, these are all included in a box near the top of the Molnupiravir fact sheet for care providers. So first, prescribers must provide an electronic or hard copy of the patient fact sheet, and must document that the patient has received the fact sheet. They must review the information contained within the patient fact sheet with the patient and counsel the patient on the known and potential benefits and risks of Molnupiravir. They must assess whether an individual of child bearing potential is pregnant or not as clinically indicated.

They should also advise regarding the need for contraception use. In individuals of child bearing potential, there should be a recommendation for contraception used for the duration of treatment and for four days after the last day of dose of Molnupiravir. For individuals who are sexually active with partners of child bearing potential, they should be advised to use contraception during treatment and for at least three months after the last dose of Molnupiravir. Prescribers must also make individuals of child bearing potential aware of the pregnancy surveillance program. And we think that this is important in the event that an individual of child bearing potential should become aware of-- that they are pregnant while they're taking Molnupiravir or shortly after completing a course of Molnupiravir so that they are potentially able to participate in the surveillance program.

Prescribers must report all medication errors and serious adverse events that are potentially related to Molnupiravir within seven calendar days of the healthcare provider's awareness of the event. And I've listed the website for electronic reporting of these events here, as well as an 800 number that can be used to report these events. And then lastly, as I noted on the previous slide, there are some unique requirements for prescribers if Molnupiravir is used in pregnancy.

Next slide, please. Here I have some helpful links.

These are the same links that you saw at the end of Dr. Troy's presentation. And these links contain a wealth of information, including access to both the patient and the healthcare provider fact sheets. All of the scientific review documents for Molnupiravir as well as other COVID-19 related products that have been authorized. And then lastly, a link for the COVID-19 therapeutics locator to help find locations and information about distribution of authorized COVID-19 products.

So thank you very much, and at this point, I will turn the presentation over to Dr. Alice Pau.

Thank you. And thanks for the organizers for the CDC to invite us to come and talk to you about the oral agents today.

Next slide, please? My name is Alice Pau, I'm the Secretary for the NIH COVID-19 Treatment Guidelines, and today I'm going to-- in the next 10 minutes or so, go through with you some of the new recommendations that our guidelines have come up with at the end of December 2021. And primarily, I'm going to focus on two major recommendations that we have. Which are the therapies for non-hospitalized patients with COVID-19, as well as some of our prioritization scheme that we have come up with based on the patient's factors.

Primarily because of the fact that we understand that we're going to be shortage of therapeutics that are available for these patients, as well as the rapidly rising of the Omicron variants during that period of time.

Next slide, please. So, the first thing we think about when we're looking at what do we want to treat patients with COVID-19 that outpatients with understanding that majority of people are either asymptomatic or with mild diseases. However, we do know that a small proportion of individuals who are at high risk of progression can progress to more severe illnesses requiring hospitalizations. Therefore, our main goal of therapy, thinking about the limited therapeutics that we have available includes the following.

Which is to prevent progression to serious disease, especially those at high risk. And by doing so, reducing the visits to urgent care setting, reducing hospitalizations and deaths. And then further to reduce potentially the duration of illness of those who are infected. And potentially reduce the infectivity and ongoing transmission of the virus, which is still an area of under investigation. And lastly, to minimize the potential of overwhelming the already overwhelmed healthcare system that we have in this country.

And given all these scopes and having that in mind, and because of the limited drug supply, our priority was the-- given really to the-- given to those who are at highest risk and receive the most benefit. Therefore, reducing the chance of them progressing to severe diseases.

Next slide, please. As you all know, before February of 2021, our recommendation really provide patients who are in the outpatient setting, despite the fact that they might be at high risk of clinical progression, to recommend primarily symptomatic management with no specific

therapy, and also direct people to go to clinical trials if they are available to them. As you know, some of the monoclonal antibody EUA started coming out in November, December of 2021.

2020. And in February of 2021 was the first time that we made specific recommendations for the outpatient settings. Initially with the first two monoclonal antibodies, which is the [inaudible] BAM+ETE. As well as [inaudible] antibodies, REGEN-COV. And then in July of 2021, Sotrovimab from the [inaudible] was also approved, had also received an EUA.

And we also make that available as the three treatment options for individuals who are in the outpatient setting.

Next slide, please. As we have heard earlier in the talk that in early December 2021, we have been seeing the increasing rise in Omicron and based on in vitro data that quickly generated and put together-- it was soon noted that potentially the two monoclonal antibodies, BAM+ETE as was REGEN-COV, would most likely not be effective against Omicron virus. And whereas Sotrovimab remains as sensitive. And on December 23rd, 2021, immediately after the issue of the EUA for Paxlovid as well as Molnupiravir with the understanding that those drugs were not yet available for the public until the next week or even the week after, we decided that we need to make some recommendations for the public in case during the Christmas holiday there are going to be a lot of individuals who may require treatment.

And therefore, Remdesivir was also added to the recommendation.

Next slide, please. And this recommendation is based on-- primarily based on in vitro data to look at the susceptibility of the different drugs for the Omicron variants. On the left hand side, you'll see this website which is the open data NCATS website. Which is updated on a daily basis to look at the potential susceptibility of the different drugs.

And what you can see is that the particles to the right hand side, the little dots that we have either from pseudo virus testing or like virus testing, the farther right you go, the less effective these drugs are. The red rectangle represents the drugs that are potentially going to be not effective, which means the two monoclonal antibody, this is similar to what Dr. Hicks has shown earlier in the graph that she had shown. And then whereas the green rectangles are the potential effective regiments. Again, these are in vitro data, we don't have clinical efficacy data to see whether they are truly effective or not.

And over time, we will be able to tell whether that is true or not. But what you can see is that there are potentially four regiments or four drugs that could be effective against the Omicron virus. And quickly, because of that, on December 23rd, the guidelines basically suggested that removing it from the list of SARS-CoV-2 monoclonal antibodies, the BAM+ETE as well as REGEN-COV, except for regions where they still may potentially be seeing a significant proportion of Delta variant at that point. So Sotrovimab became the only recommended anti-SARS-CoV-2 monoclonal antibody, and Remdesivir for three days was now added to the potential options. And that is primarily based on an outpatient clinical trial looking at placebo versus Remdesivir for three days in the PINETREE trial to show efficacious effects in reducing hospitalization and death.

And also, this occurred because of the limited supply of Sotrovimab and also because Molnupiravir [inaudible] not available yet for general use.

Next slide, please. Next slide. A week later on December 30th, the panel come up with two new statements that most of you are probably aware of. The first statement was primarily looking at all the different regiments that are currently available and we tried to give the clinicians guidance as to how to use these therapies.

The second one was a statement primarily focused on drug-drug interactions with Paxlovid-Ritonavir boosted Nirmatrelvir.

Next slide, please. So for the first time, the panel actually come up with a preference list. That listed in here with Paxlovid being number one, followed by Sotrovimab, followed by Remdesivir, and followed by Molnupiravir.

Next slide.

So the question is how do we come up with these recommendations that for the first time we are preferentially choosing some drugs over another? And when we are trying to think about how to differentiate between these agents, the far most important thing to us is clinical efficacy of these stages. And in terms of the ability to reduce hospitalizations and deaths in these populations, based on the data that we have seen in clinical trials with the understanding that all these clinical trials were primarily done prior to vaccination as well as prior to the Omicron virus variant. But secondly is how convenient and how logistically possible is it for us to be able to deliver these drugs to the patients with understanding that some of them are orally available but others require IV infusion in an infusion center, and the duration of therapy really varies from drug to drug. And thirdly, we look at the availability to populations that are of interest. With include children as well as pregnancy.

And lastly is the drug interaction potential.

Next slide, please. So looking at that first thing that we look at is clinical efficacy. On this graph, you can see the relative risk reduction in terms of reducing hospitalization and death. And you can see that the first three drugs are pretty much head to head comparing with placebo in reducing by over 80% of the cases.

Whereas, as you can see on the far right is Molnupiravir, which is much, much lower in terms of this efficacy. Therefore, our recommendation is primarily is that the first three choices are the most important choices and Molnupiravir will only be recommended if the other three choices are not available.

Next slide, please. So this table basically is to give you a comparison to summarize some of the things that we have already sent. Going from left to right is the ranking of the different regiment.

As you have seen, with regards to age, the first three drugs are now approved for children between the age of 12 and 17, whereas Molnupiravir is only approved for 18 years or older. The

initiation, when to give these agents, really varies. Depends on how the clinical trials were being conducted. With the oral agents, using within five days of symptom onset, whereas Sotrovimab within 10 days, and Remdesivir within seven days. As we have said already, both Sotrovimab and Remdesivir requires IV infusion.

And there's a difference between them because Remdesivir requires three days of IV infusion, meaning that individuals have to go to the clinical-- to the center to get the infusion three times. So, the-- as far as advantages [inaudible], most of them are very highly efficacious, whereas Molnupiravir is the lowest in efficacy. As far as the disadvantage, as you can see, Paxlovid, the primary disadvantage is the drug-drug interaction. And Sotrovimab with Remdesivir was requiring IV infusion. And then with Molnupiravir is the ability to use it in children or pregnancy.

And then there's a potential, but probably low concern, of mutagenicity. But lastly is probably the most important is the availability of these supplies. And as we know, as of right now, still we have a limited supply for Paxlovid as well as Sotrovimab. Remdesivir is commercially available. Molnupiravir is a much greater supply at this point when compared to Paxlovid as well as Sotrovimab.

Next slide, please. So, because of all these concerns with unequal prioritization on December 23rd, a week before these other drugs became available, we came up with another recommendation, basically is to say how to prioritize the patient based on the potential of logistical as well as supply constraints.

Next slide, please. So basically when do we prioritize? Obviously if the demands far exceed the supplies. If there are logistical issues, in this case we would not be able to provide IV therapy for some of the patients.

Because it involves personnel, space, equipment, and time slots. And lastly, if there is cost related issues.

Next slide, please. So with that, our goal of this particular statement is based on the fact that we indicated that when resources are limited, we want to provide therapy to individuals who may derive the most benefit from the treatment. And in this case, it would be those people who are at the highest risk for progression to severe or critical disease.

And the reasons are the ones that I stated earlier because of the rapid rise of COVID-19, because of the fact that Sotrovimab was only monoclonal antibody that is now available for use. As well as the short supply of the other drugs. So the number of factors that we take into account when we try to come up with this recommendation is based on how significant these individuals might be-- may progress to serious disease. Definitely older individuals are more likely than younger individuals, those who are unvaccinated are unable to mount a good response to vaccines are more likely than vaccinated, those with several immunocompromised state are more likely than immunocompetent. Individual clinical factors such as obesity, diabetes, and cardiovascular disease.

And obviously in those who has multiple risk factors are at higher risk than the others.

Next slide, please. So this is a prioritization risk-- list that we have in the guidelines that you can go to. It's somewhat complicated, but the bottom line is that we prioritize them by different tiers, with the first tier being those who are immunocompromised and not be able to mount a good response to vaccine or that if they have the infection, they may have more serious disease. Or those who are unvaccinated but also at high risk of severe disease.

So in immunocompromised cases, regardless of the vaccination status, and then go all the way down to the last group would be those who are vaccinated but at risk of severe diseases. These include individuals who are older than 65, or those who are less than 65 years of age and have clinical risk factors.

Next slide. So this would not have happened without the work of many of the clinicians around the country and academic individuals. And we work very hard over the last almost two years to get the guidelines out to the public.

And with that, I'm going to pass it on to the moderator.

Presenters, thank you so much for providing our audience with this timely information. We will now go into our Q&A session. In addition to our presenters, we would also like to welcome CDC subject matter experts, Dr. Emily Cummins, Dr. Beth Schweitzer, and from FDA Dr.

John Farley to our Q&A session. Thank you all for joining us. Please remember, for our audience to ask a question using Zoom, click the Q&A button at the bottom of your screen. Then type your question. Our first question asks does antiviral treatment affect how long a person with COVID-19 should be isolated?

Hi, this is Lauri Hicks. I can take that question. I think the short answer is no? But the longer answer is that data are very limited regarding whether there are differences in SARS-CoV-2 transmission and people treated with antivirals compared to untreated people. And there really aren't any data at this time to support a different isolation period for people treated with antivirals. And I think there will be more discussion about updates to quarantine and isolation on our COCA call tomorrow, which will encompass both healthcare and non-healthcare settings.

So I would encourage you to consider joining that call as well if you're interested in that topic.

Thank you very much for that. Our next question is about the therapeutic options we talked about. The question asks how can we find out more about supplies of Paxlovid, Sotrovimab, or Molnupiravir in their practice areas?

[Inaudible] Colin Shepard. I would just encourage you to go to the ASPR website, Assistant Secretary for Preparedness and Response. There's information on each drug. It's phe.gov.

And that has some additional information. You can also email COVID19Therapeutics@HHS.gov. We do-- we also have a COVID therapeutics locator website that's recently launched that

can help find treatment locations. And then since it is at this time a state and territory health department directed distribution system, your state or local health department may have some specific information online.

Thank you, Dr. Shepard. And for our audience, a lot of these links can be found on the additional resources section of today's COCA's call webpage. As well as where the slides will be posted and you'll be able to follow some of these links there. Our next question asks how can a provider choose from these various antiviral therapies that are authorized for the outpatient management of COVID-19?

Well, I guess I can answer that because we come up with our recommendations based on the different available regiments that are available. So, I think one can see, as I mentioned earlier in the graph that I had shown, is that as far as clinical efficacy's concerned, [inaudible] Sotrovimab as well as Remdesivir are all very highly effective. In the clinical trials that were done in reducing hospitalization and mortality. The choice really comes down to what is available in your area, what are the logistics of getting an IV infusion for your-- or even three IV infusion for your patients. You know, in your area.

And whether there are significant drug-drug interactions that might prohibit you from using Paxlovid. And I think at least in the area where I am, the main limiting factor is really supply at this point. In general, Molnupiravir is the last choice, because of its much lower efficacy and also, you know, obviously it is not recommended for children as well as for pregnant individuals.

Thank you very much. Our next question sort of is one that we're seeing a lot. You've talked about efficacy for therapeutics. But specifically for the oral products, Paxlovid and Molnupiravir, how do they compare when it comes to the Omicron variant? Can you speak about that?

Hi, this is Stephanie Troy from FDA. And I can take that for Paxlovid. As I mentioned in my talk, there's no clinical data on the activity Paxlovid against Omicron. But preliminary biochemical and cell culture data indicate that Nirmatrelvir retains activity against the Omicron variant. And I will pass it off to Dr. Hodowanec for Molnupiravir.

Hi, thank you. This is Aimee Hodowanec. So, for Molnupiravir, as was the case with Paxlovid, the trials were conducted before Omicron was circulating, so we don't have clinical data regarding this. But similarly, there are preliminary reports of in vitro data that show that Molnupiravir retains its activity against the Omicron variant. And this is what we would expect sort of based on the mechanism of action of Molnupiravir in the conserved drug target across different variants.

Thank you very much. Our next question asks is Molnupiravir mutagenic to patients?

This is John Farley from FDA, I can take that question. So, so based on the available data, and the short five-day treatment course, FDA assessed the risk of mutagenicity to patients as low. And I would refer folks who want more detail to our Molnupiravir review, which is public. And that is on the last of Dr. Hodowanec's slide, that link.

Thanks.

Thank you very much. And again, the slides are posted on the COCA call's webpage. And we will share that link with you so everyone can access those slides. Our next question asks is there a risk of HIV 1 resistance development in patients taking Paxlovid?

Hi. This is Dr. Troy again, and I can take this question. Because Nirmatrelvir is co-administered with Ritonavir, which at higher doses is an HIV protease inhibitor, there may be a risk of HIV developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV infection. So, patients with HIV who are not on treatment and who do not have undetectable viral load should talk with their healthcare provider before taking Paxlovid.

Thank you.

Thank you very much. We have time for one last question. And the question asks-- it comes from a provider who's not familiar with using Ritonavir and wants to know what are some important steps before prescribing Paxlovid, which is the combination, for their patients. Considering Ritonavir's in it.

So, this is Alice Pau. I think I can take this one. Mainly-- one thing is that-- one thing I didn't show you is that there is another compendium page that we put together which involves the recommendation for how to use it in patients, particularly Ritonavir and other concomitant medications, which could have a potentially drug-drug interaction potential. And one thing to note is that the five-day drug interaction is very different from taking the drug chronically. So, in some cases, despite the fact that some of the drugs may have significant interaction that you may want to avoid it, you-- it may not totally be the case where you're using it for five days.

So the one thing that is the most important thing is before prescribing Paxlovid, especially in the outpatient setting, is to get the list of medications the patient's on. And look through them and see whether there is any potential interaction. There is a number of different guides that are currently available. We have the list that we have in the guidelines, but also, you know, there is an interactive internet guide that one can go to, which is the interaction guide from the Liverpool Group. And if one needs to, I can send that out as well.

And also, the packages there provide a number of, you know, potential recommendations for what can be used and what cannot be used. You know, particularly in those cases where a drug that could have a very narrow toxicity profile where it significantly increases the concentration of the competing drug may be harmful. Those are the cases where you do not want to use Ritonavir.

Thank you very much for that. With that, I want to thank everyone for joining us today, with a special thanks to our presenters and our subject matter experts. Please note that today's COCA call will be available on demand a few hours after the live call. You can find the video recording of today's COCA call, as well as the materials we talked about, such as slides, at emergency. cdc.

gov/coca. Again, that's emergency. cdc. gov/coca. Please join us for our next COCA call tomorrow, Thursday, January 13, from 2 pm to 3 pm Eastern.

The topic will be Updates to CDC's COVID-19 Quarantine and Isolation Guidelines in Healthcare and Non-Healthcare settings. That COCA call again is tomorrow, Thursday, January 13 from 2 pm to 3 pm Eastern. Please continue to visit emergency. cdc. gov/coca to get more details about upcoming COCA calls as we intend to host more COCA calls to keep you informed of the latest guidance and updates regarding COVID-19.

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