Washington State Pharmacy and Therapeutics Committee
Drug Utilization Review Board
Meeting Transcription
February 16, 2021

Leta Evaskus: Jordan, why don't we go ahead and convene the meeting. So if you can read off the list of participants in the meeting to do a roll call. And then for the agenda, we are going to skip the first agenda item that Donna was going to go over the P&T and DUR process overview, and we will just jump into Atopic Dermatitis.

Jordan Storhaug: Okay, so we will get started here. We will now convene the P&T Committee meeting. I am Jordan Storhaug, the Chair of the P&T Committee. We do have two new members, Laura Beste and John MacKay. I might just give them an opportunity after we do the roll call to introduce themselves then. And first, we will just run through the roll call. So after I call everybody's name, if you would just be able to say "here" so we can know who is here. So starting with the P&T Committee Members first off is Virginia Buccola.

Virginia Buccola: Good morning. I am here.

Jordan Storhaug: Next is Diane Schwilke.

Diane Schwilke: Good morning. I am here.

Jordan Storhaug: Leah Marcotte.

Leah Marcotte: Good morning, here.

Jordan Storhaug: Susan Flatebo. Kavita Chawla.

Kavita Chawla: I'm here. Good morning.

Jordan Storhaug: Laura Beste.

Laura Beste: Here.

Jordan Storhaug: Perfect. Jon MacKay.

Jon MacKay: Good morning. I'm here.

Jordan Storhaug: Good. And Alex Park and Michael Corsilles are absent today. For our Health Care Authority Members, Leta Evaskus.

Leta Evaskus: Here.

Jordan Storhaug: Donna Sullivan.

Donna Sullivan: Good morning, Jordan. I'm here.

Jordan Storhaug: Good. Ryan Pistoressi.

Ryan Pistoressi: Here.

Jordan Storhaug: Marissa Tabile.

Marissa Tabile: I'm here.

Jordan Storhaug: Luke Dearden.

Luke Dearden: Here.

Jordan Storhaug: Ryan Taketomo. Amy Irwin. Joey Zarate.

Joey Zarate: I'm here.

Jordan Storhaug: For the Drug Effectiveness Review project presenters, Wesley Lindsey, Courtney Gamston.

Leta Evaskus: I haven't enabled all of their mics yet, so you can just run through their names, but don't wait for a response.

Jordan Storhaug: Okay. Thanks. Roz Kelly, Shannon Robalino, and Andrea Vintro. For Magellan Medicaid administrative presenter, we have Umang Patel.

Umang Patel: I am here.

Jordan Storhaug: Perfect. All right. For the Managed Care Organization Representatives, Greg Simas of Molina Healthcare.

Leta Evaskus: I also haven't enabled their mics, so you might just want to run through that list.

Jordan Storhaug: Heidi Goodrich of Molina Healthcare, Petra Eichelsdoerfer of United Healthcare, Omar Daoud of Community Health Plan of Washington, and Geoffrey Natividad of Community Health Plan of Washington. I wanted to come back and give the opportunity for our two new Committee Members to introduce themselves. So first, Laura, would you be able to introduce yourself to the group?

Laura Beste: Yes, good morning. I am Laura Beste. I am a Clinical Pharmacist at Allenmore Hospital, part of MultiCare Health System, and I am glad to be able to participate. Looking forward to it. Thank you.

Jordan Storhaug: Laura, thank you and welcome. And then Jon, would you be able to introduce yourself to the group?

Jon MacKay: Sure. Good morning. My name is Jon MacKay. I am a Pharmacy Director with Native Project. We are in the Urban Indian Healthcare Center, CHC in Spokane, Washington. I spent most of my career in ambulatory care. I have worked with CHC pretty extensively, and my most recent position as far as Director is with Native Project.

Jordan Storhaug: Very good. Welcome to the crew. So then, after a late start, we will get going here. And our first topic will be [cross-talk] --

Leta Evaskus: Oh, Jordan.

Jordan Storhaug: Yeah.

Leta Evaskus: Sorry to interrupt you. This is Leta Evaskus. Let me just go over the meeting logistics.

Jordan Storhaug: Yes, absolutely. Thank you for interrupting me.

Leta Evaskus: No problem. Okay, I am very sorry for the technical difficulties that we are having today. So the Committee Members should all be able to mute and unmute themselves. For the stakeholders, I will unmute you when you are called on. And you can use the raise hand function if you are not on the pre-

registered list. You will have three minutes to speak. Presenters, please share your webcams when presenting, and the Committee, you can share your webcams when you are deliberating on the motion. So, for the stakeholders, the Chair is first going to read through the pre-registered speakers, and I will have to unmute you and then disable your mic, so please give me a minute if there is a pause. And you could also put questions in the chat function.
But I am going to ask that stakeholders do not continue entering in the chat during the motion deliberation. We cannot turn the chat off. So I don't want the committee to be distracted by stakeholders making comments when it is not the stakeholder comment period. And the meeting is being recorded, so please state your name every time you speak. This will be transcribed afterward, and that makes it best for identifying who is speaking. And with that, I will turn it back to you, Jordan.

Jordan Storhaug: All right, perfect. Thank you, so much. And so with that, I think we are ready for Atopic Dermatitis. Just turning it over to you, Wesley Lindsey from DERP.

Leta Evaskus: Okay. Let me share my screen. Okay, is Wesley unmuted?

Wesley Lindsey: All right. Now, it looks like it is giving me the ability to unmute. Can everybody hear me?

Leta Evaskus: Yes.

Jordan Storhaug: I can't hear you [indistinct].

Wesley Lindsey: Great. All right. Well, actually, I think maybe we have been trying to reach out to you. If there could be the possibility of swapping the presentations today for atopic dermatitis and the biologics for non-asthma indications, my colleague -- just because of the time changes -- she has a little bit earlier deadline in the day, and I have a little bit more flexibility. So could there be any possibility of making that change?

Leta Evaskus: Yes, we can do that. Let me change slides here.

Wesley Lindsey: I know everybody is really excited to hear about atopic dermatitis, but we are going to have to maybe just hold on for a little bit longer.

Leta Evaskus: Okay, so biologic drugs for non-asthma?

Wesley Lindsey: Yes, please.

Leta Evaskus: Okay. Okay. And Laura, can you check that Courtney Gamston is enabled to speak?

Courtney Gamston: Yes. I'm ready for the State, okay?

Leta Evaskus: Okay, let me share my screen again.

Courtney Gamston: And thank you for making this change.

Leta Evaskus: Oh, no problem.

Courtney Gamston: To accommodate my schedule.

Leta Evaskus: I am sorry that we had difficulties today. My computer is being slow, so just a minute until it allows me to present here.

Courtney Gamston: And just one question. How should I advance slides or ask you to advance slides?

Leta Evaskus: You can just say Next slide, and I will move it.

Courtney Gamston: Alright, thank you.

Leta Evaskus: Okay, there we go.

Courtney Gamston: All right. Thank you. My name is Dr. Courtney Gamston, and on behalf of my team, I am presenting this review of biologic drugs for non-asthma-related indications. Next slide. And so this review will follow the same general format as previous DERP reviews. Next slide, please. I wanted to start off with a list of abbreviations that are included throughout this presentation. There are several included disease states, and for many, specific tools are utilized to assess the disease state. So this slide includes a collated list, but they are also spelled out on each of the slides on which they are included. Next slide. So the use of biologic drugs in asthma was analyzed in a previous DERP review, and the biologic drugs that are used to treat asthma may also be of benefit in non-asthma inflammatory conditions that are associated with diminished physical health and quality of life. These include chronic spontaneous urticaria (CSU), eosinophilic granulomatosis with polyangiitis

(EGPA), hypereosinophilic syndrome (HES), chronic rhinosinusitis (CRS), and chronic rhinosinusitis with nasal polyps. The currently available treatment options for each of these conditions do not fully alleviate symptoms in some patients and may result in undesirable adverse effects. Next slide. CSU is also known as chronic idiopathic urticaria and is caused by histamine release from mast cells that are activated by IgE, resulting in recurrent hives and/or wheals with or without angioedema. It is generally self-limiting but negatively impacts quality of life. Current treatments include antihistamines. EGPA was formerly known as Churg-Strauss syndrome and is a multi-system disease caused by activation of the IL-5 receptor that leads to the proliferation of eosinophils. It is somewhat progressive and can affect one or more [indistinct] and organs. Without treatment, EGPA can be fatal. The current treatment for EGPA is systemic corticosteroids. HES is rare and characterized by continuous overproduction of eosinophils due to activation of the IL-5 receptor. Release of inflammatory mediators and infiltration cause organ damage. In some cases, this condition is also fatal. Systemic corticosteroids are the current treatment for this condition. Next slide. CRS is a common inflammatory condition that affects the paranasal sinuses and lining of the nasal passages. There are two subtypes: CRS with nasal polyps and CRS without nasal polyps. Nasal polyps are tumor-like swellings within the nasal mucosa. The current treatment for both subtypes of CRS is intranasal corticosteroids. Systemic corticosteroids are used for severe symptoms or exacerbations, and surgical removal of polyps is also employed, but recurrence is common. Next slide. The populations of interest vary by the biologic agent reviewed. For dupilumab, we focused on adults with inadequately controlled CRS with nasal polyps. For mepolizumab, we reviewed the literature for studies including adults with EGPA participants 12 years of age and older with HES with no identifiable cause for at least six months and adults with CRS with nasal polyps with an inadequate response to intranasal steroids. For omalizumab, the population of interest included participants aged 12 years and older with symptomatic CSU despite histamine therapy and adults with nasal polyps with an inadequate response to intranasal steroids. Next slide. We reviewed three biologic medications. The table on this slide outlines the FDA-approved indications related to this review. So dupilumab was approved in March 2019 as add-on maintenance therapy for adults with inadequately controlled CRS with nasal polyps. Mepolizumab was approved for adults with EGPA in December of 2017. For individuals aged 12 years and older with HES without an identifiable nonhematologic cause for at least six months in September of 2020, and in July of 2021, it was approved as add-on maintenance therapy for adults with

CRS with nasal polyps that were inadequately controlled with intranasal steroids. Omalizumab was approved in March 2014 for individuals aged 12 years and older with symptomatic CSU despite antihistamine therapy. And in November of 2020, as add-on maintenance therapy for adults with nasal polyps inadequately controlled with intranasal steroids. Slide. This table summarizes the activity of the reviewed medications and the disease states for which they were reviewed. All three are monoclonal antibodies. Dupilumab specifically targets IgG4, which inhibits IL-4 and IL-13, leading to inhibition of the release of proinflammatory mediators. This review assessed the evidence for use in CRS and CRS with nasal polyps. Mepolizumab is an IL-5 antagonist, which prevents the differentiation recruitment and activation, and survival of eosinophils. We assessed the evidence for use in CRS, CRS with nasal polyps, EGPA, and HES. Omalizumab is an anti-IgE antibody that inhibits IgE binding on immune cells, leading to a decrease in eosinophils and inflammatory mediators, including IL-4, IL-5, and IL-13. Next slide. The criteria for this review included several comparators, though all identified eligible studies compared the biologic medications to placebo. We reviewed only randomized controlled trials. Next slide. The outcomes of interest included symptom control, quality of life, the occurrence of severe exacerbations, hospital admissions, and a list of condition-specific outcomes as listed on this slide. We also reviewed harm outcomes, including mortality, adverse events, and serious adverse events. Next slide. The key questions for this review included examination of the effectiveness of the included biologic drugs and the harms associated with the use of these medications for the included indications. And the characteristics of ongoing studies for the use of these biologic agents for the treatment of the included disease states. Next slide. So now we are going to shift gears and discuss the methods for this review. Next slide. The reviewed evidence sources included Medline, the Cochrane Library, and Google Scholar. We also reviewed ongoing studies through ClinicalTrials.gov, the FDA, and utilizing the International Standard Randomized Controlled Number. Next slide.And this review was completed in accordance with the methods of the previous DERP reviews. Next slide.The risk of bias was assessed as low, moderate, or high based on reporting of methods, potential biases, and conflicts of interests. In order to receive a rating of low, the methods must have been clearly reported, potential biases must have been mitigated, and conflicts of interest must have been absent or insignificant. Next slide.We assessed the certainty of evidence using the grade criteria for numerous outcomes related to the use of biologic medications, and they are listed across the top. Next slide. Alright, now we will move into findings. Next slide. We identified a total of 88 studies and

excluded 51 of these studies; 37 full-text documents were assessed for eligibility, 10 of which were excluded from the analysis due to not being within the scope of this review. We evaluated nine new documents and 18 documents that were carried forward from the DERP Review of Biologic Medications and Asthma. Next slide. If you will go back, yes, thank you. We reviewed a total of 10 publications for CSU, all of which focused on the use of omalizumab. This included eight randomized controlled trials, one additional report of study data, and one subgroup analysis. We reviewed two publications for EGPA, both of which examined the use of mepolizumab. This included one randomized control trial and one post hoc analysis. There were three included publications for HES, all of which examined mepolizumab. This included two randomized control trials and one subgroup analysis. Next slide. For CRS and CRS with nasal polyps, 12 publications were included in the review. All three biologics of interest were reviewed within these 12 publications. For omalizumab, there were three randomized control trials, there were two randomized controlled trials for dupilumab, [indistinct] additional reports of study data in two subgroup analyses also included. And for mepolizumab, we reviewed three randomized controlled trials. Next slide. For ease of understanding, we grouped the findings by disease state instead of by medication. Next slide. There were several instruments used to assess CSU. They are listed here, and you will see them throughout the next several slides. They included the Urticaria Activity Score (UAS) and weekly urticaria activity score, for which a higher score indicates increased disease activity. The weekly Itch Severity Score, for which a higher score also indicates an increased severity. The Dermatology Life Quality Index and Chronic Urticaria Quality of Life are also included, for which a lower score indicates a better quality of life. And the Angioedema Activity Score, a higher score there indicates increased disease state activity. Next slide. I will provide a brief summary for each of the slides containing study-specific information. In each of these slides. The first column provides the publication information. All of the included trials were randomized controlled trials, which can be seen in the second column along with the number of participants in each trial. Their intervention and primary outcomes are listed in columns three and four, respectively. Column five includes the study duration, and the risk of bias appears in column six. For the majority of the included studies, the risk of bias was rated as moderate. This slide and the next two slides contain the information about the [indistinct] included studies for CSU. Every study evaluated the use of omalizumab. The three studies listed here included 49 to 336 participants and evaluated omalizumab 75 mg to 375 mg given subcutaneously every two to four weeks depending on dose and range from

27 to 40 weeks in duration. Primary outcomes included change in the weekly urticaria activity score from baseline. Change in the itch severity score from baseline and frequency and severity of adverse effects. Next slide. The next three studies and one report of additional study data enrolled 30 to 319 participants and evaluated omalizumab 75 mg to 300 mg given every four weeks. These studies spanned 20 to 40 weeks and evaluated the change in itch severity score, change in the chronic urticaria quality of Life questionnaire, or change in the concentration of the high-affinity IgE receptor or IgE-positive skin cells from baseline. Next slide. The two studies in one subgroup analysis included on the slide included over 100 participants each and compared 150 mg to 300 mg of subcutaneous omalizumab every four weeks to placebo. Study duration was 26 to 40 weeks. One of the studies evaluated the change from baseline in the weekly itch severity score while the other examined the percentage of participants with clinical worsening as measured by an elevated weekly urticaria activity score for at least two consecutive weeks. Next slide. The first outcome of interest in the top half of the slide was the change in that weekly urticaria activity score. The Minimally Clinically Important Difference (MCID) is 9.5 to 10.5 based on the literature. Seven randomized controlled trials for the use of omalizumab included 1500 participants that were reviewed for this outcome. The evidence was graded as moderate, and omalizumab was found to be superior to placebo. At 300 mg, the mean treatment difference ranged from negative 8.6 to 12.8 versus placebo. At 150 mg, the mean treatment difference ranged from negative 4.9 to negative 6.5 versus placebo. The second outcome of interest was the change in the weekly itch severity score. The MCID for this total was not found within the literature. We evaluated for randomized controlled trials with omalizumab as the subject medication that included a total of 860 participants. The evidence was graded as moderate and omalizumab was found to be superior to placebo. The 300 mg dose was associated with the main treatment difference of negative 3.7 to negative 5.8 versus placebo, and the 150 mg dose was associated with a mean treatment difference of negative 2.3 to negative 3.0 versus placebo. The authors also tested a 75 mg dose, but this dose rarely produced a statistically significant difference when compared with placebo. Next slide.

The next outcome of interest was changed in the dermatology life quality index, which has an MCID of 4. This outcome was evaluated in seven randomized controlled trials of omalizumab and included 1132 participants. The evidence was graded as moderate, and omalizumab was found to be superior to placebo. At a dose of 300 mg, the main treatment difference was negative 3.1 to negative 4.7 versus placebo. At 150 mg, the mean treatment

difference was negative 1.9 to negative 2.5 versus placebo. For adverse events, we reviewed seven randomized controlled trials for their use of omalizumab, which included 1366 participants. The evidence was graded as low. The results suggested a similar occurrence of adverse effects for participants in both the omalizumab and placebo groups. Next slide. So now, we will cover the evidence regarding EGPA. Next slide. There were only two identified publications that examined the use of one of the biologic medications of interest for EGPA. There was one trial and one post hoc analysis of trial data. There were 136 participants, and the use of mepolizumab 300 mg administered subcutaneously every four weeks was compared with a matched placebo. The primary outcomes included total accrued weeks of remission and the proportion of participants with remission at both weeks 36 and 48 in the study span of 60 weeks. Next slide. For the outcome of remission, one randomized controlled trial examining the use of mepolizumab included those 136 participants, as mentioned on the slide previously, and the evidence was graded as low. The evidence demonstrated increased accrued time in remission compared to placebo; 28% of participants in the mepolizumab group compared with 3% of participants in the placebo group achieved at least 24 weeks of accrued remission, resulting in an odds ratio of 5.91. Next slide. The same study evaluated the outcome of relapse. That evidence was assessed as low and demonstrated that delayed occurrence of the first relapse in participants in the mepolizumab group compared with placebo, and 56% of participants in the mepolizumab group compared with 82% of participants in the placebo group experienced a relapse during the trial period. For the outcome of adverse events within the same study, the evidence was graded as moderate, and no statistical difference in adverse effects was found between mepolizumab and placebo groups. Next slide. Alright. And now we will take a look at HES. Next slide. For HES, two trials were identified as well as one subgroup analysis. The interventions consisted of either mepolizumab 300 mg administered subcutaneously or a 750 mg infusion each given every four weeks for either 32 or 36 weeks. The primary outcomes included the reduction in daily prednisone use or the proportion of participants with a flare occurrence within the study period. Next slide. For the outcome of a dose reduction for systemic corticosteroids, for mepolizumab in one randomized controlled trial, including 136 participants, the evidence was graded as moderate, and it was found that mepolizumab significantly reduced the use of prednisone dose during the treatment period when compared with placebo at a rate of 84% in the mepolizumab group and 43% in the placebo group, with a hazard ratio of 2.90. Next slide. For the outcome

of time to first flare occurrence, in that same population, the evidence was graded as moderate, and it was found that in the mepolizumab group the occurrence of flares was 50% lower than with placebo. With regard to adverse events, the evidence was rated as low, and statistical analysis was not performed on treatment-related adverse effects, and generally, the adverse effect occurrence was similar between the treatment and placebo groups. Next slide. So we will move into our last disease state, and this is CRS and CRS with nasal polyps. Next slide. For CRS and CRS with nasal polyps, there are several assessments and questionnaires utilized to assess disease state, status and control, symptomology, and quality of life. The Nasal Polyp SCORAD Total Polyp Score assesses the occurrence of obstruction of nasal polyps with a higher score indicating worse disease state status. The nasal congestion score is a measure of symptomology with a higher score indicating worse disease state status in the Short Form Health Questionnaire, Asthma Quality of Life Questionnaire, and Sino-Nasal Outcomes Test all assess quality of life. Though higher scores for the SF-36 and AQLQ indicate a better quality of life and a lower score for the SNOT-20 to indicate better disease control and quality of life. For the University of Pennsylvania Smell Identification Test, a higher score indicates a better sense of smell. And the one Mackay CT score assesses opacification of the sinuses with a higher score indicating higher opacification and worse disease state, or control, or severity. Next slide. For the studies examining the use of biologics in CRS, we organized the studies by individual agents. So on this first slide, the three listed studies included 14 to 265 participants, and the intervention consisted of omalizumab based on body weight and serum IgE that range from 75 mg to 600 mg and was administered subcutaneous every two to four weeks depending on the dose. These studies span 16 weeks to six months, and the primary outcomes included change from baseline in nasal polyp score, total polyp score, nasal congestion score, or sinus inflammation. Next slide. There were two studies identified that evaluated the use of dupilumab as well as one post hoc analysis, one subgroup analysis, and two additional reports of study data. There were 60 and 1902 participants in the two trials. They evaluated dupilumab 200 mg or 300 mg, and one of the trials gave a loading dose. The primary outcomes included annualized severe asthma exacerbation rate. Because this was a post hoc analysis of an asthma trial and change from baseline in pre- and post-bronchodilator FEV1. For the second trial in the two additional data reports, the primary outcome was change in bilateral nasal polyps score from baseline to study end at 16 weeks, and the other trial lasted for 52 weeks. Next slide. For the trial and subgroup analysis listed on this slide, there were 724 participants and then a subgroup of 49

participants that were evaluated. The intervention included dupilumab 300 mg every two weeks for 52 weeks or every two weeks for 24 weeks, followed by every four weeks for 28 weeks. Primary outcomes included change in NPS and change in NCS at 24 weeks and change in the Lund-Mackay CT score at 24 weeks. The studies lasted for 48 weeks and 64 weeks. Next slide.
There were three studies that examined the impact of mepolizumab on CRS and CRS with nasal polyps. They included 30 to 407 participants and investigated the use of 100 mg of mepolizumab administered subcutaneously or 750 mg via IV infusion every four weeks. Primary outcomes included change from baseline in that total polyp score, change in the Nasal Obstruction Visual Analog Scale (VAS) during weeks 49 through 52, and the number of patients or participants that were no longer candidates for nasal polyp surgery based on NPS and the VAS, these studies lasted for 25 to 52 weeks. Next slide. The evidence for change from baseline in the nasal polyp score for omalizumab comes from the two randomized control trials that included 303 participants. Actually, can you go back one slide? I am a little bit out of order here. All right. Go down one slide. Alright. So when we are looking at the change from baseline in that FEV1, we are looking at dupilumab three included randomized controlled trials that included 2686 participants. The evidence was graded as moderate, and it was found that dupilumab inconsistently improved the FEV1 from baseline compared with placebo. That mean change range was from 0.12 to .34 liters. With regard to change from baseline in that total polyp score, mepolizumab in three randomized controlled trials including 551 participants demonstrated that more participants achieved a significant reduction in that total polyp score compared with placebo. The treatment difference range was from negative 0.9 to negative 1.3, and that evidence was graded as moderate. Next slide.
The evidence for change from baseline and the nasal polyp score for omalizumab comes from two trials that included 303 individuals. The evidence was rated as moderate and demonstrated that omalizumab significantly improved that nasal polyp score compared with placebo. That mean treatment difference range was negative 0.59 to negative 1.14, and it was found that there was a one-point or greater improvement in that nasal polyp score in 56.3% of the omalizumab treated group compared with 28.7% of individuals in our participants in the placebo group for the change from baseline in the nasal congestion score, and this was evaluated in one randomized controlled trial for omalizumab and encapsulated 265 participants. The evidence was graded as moderate, and it was found that omalizumab significantly improved that nasal congestion score compared with placebo, with a mean treatment difference range of negative 0.5 to

negative 0.55. Next slide. So on this slide, we are looking at the same outcomes but for the use of dupilumab. So for dupilumab in two randomized controlled trials and 844 participants, the evidence was graded as moderate, and it was found that dupilumab significantly improved that nasal polyp score compared with placebo. With regard to change from baseline in that nasal congestion score, there was one included randomized controlled trial for dupilumab, which encompassed 784 participants. The evidence was once again graded as moderate, and it was found that dupilumab significantly improved that nasal congestion score compared with placebo. Next slide. For the reduction in the SNOT score, there were two different versions of the SNOT score that appeared in these trials, the SNOT-20, or the SNOT-22. The MCID was 8.9 for omalizumab in two randomized controlled trials in 279 participants. Moderate grade rating of evidence found that omalizumab use was associated with a significant SNOT score reduction compared with placebo. The SNOT-22 treatment difference was negative 21.59 to negative 24.7 versus placebo, and for SNOT-20 that mean change in the intermediate score was negative 1.05 versus negative 0.2 versus placebo. For dupilumab, there were three randomized controlled trials that assessed this outcome, which included 2686 individuals. Again, the evidence was rated as moderate, and dupilumab was found to significantly reduce the SNOT score compared with placebo. At 16 weeks, that treatment difference was negative 18.1 versus placebo. At 24 weeks, it was negative 10.32 to negative 21.12 versus placebo. And at 52 weeks, it was negative 11.5 to negative 20.96 versus placebo. Next slide. And for mepolizumab, with regard to the same SNOT-20, SNOT-22 outcome, in one randomized controlled trial and 414 participants, it was found that mepolizumab use was associated with a significant score reduction compared with placebo. This evidence was graded as high, and that treatment effect was negative 16.49 versus placebo. Next slide. With regard to the SF-36, I wanted to start by taking a look at the different domains. So the domains are listed here, and each has its own MCID. So we have the physical functioning role limitations with regard to physical health, role limitations with regard to an emotional area, vitality, emotional well-being, social functioning, pain, and general health. Next slide, please. And it is important to break it down by domain because there were differences in some domains but not in others. So with regard to improvement in that SF-36 or omalizumab in two randomized controlled trials in 38 individuals. Omalizumab improved specific domain scores compared with placebo, and those included the physical health domain, which improved in one study, and the vitality domain, which improved in one study. For dupilumab, in one randomized controlled trial with 60 participants, dupilumab improved

specific domains as well. It was found that there was significant improvement in five domains: general health, physical functioning, role physical, social functioning, and vitality versus no improvement in the placebo group. Next slide. There are also multiple domains for the asthma quality of life questionnaire, which includes symptoms, activity limitation, emotional function, and environmental stimuli. Next slide. For the AQLQ, the MCID is 0.5 for omalizumab in two trials, including 289 participants. Evidence once again was rated as moderate. And it was found that omalizumab significantly improved the AQLQ compared to with placebo, specifically within the domains of activity limitations, symptoms, and emotional function. For dupilumab in the one trial including 1902 individuals, dupilumab significantly improved the AQLQ score compared with placebo at 52 weeks. And you can see the difference in the mean differences at the two different doses that were utilized, the 200 mg and the 300 mg doses. Next slide. With regard to adverse events for omalizumab in the two included trials and 303 participants, we found that there were mild adverse effects that were common, but they occurred at a similar rate compared with placebo, and common cold was the only adverse effect to occur more often in the omalizumab group. For dupilumab, in two trials and 844 participants, mild adverse effects were common, but there were no differences found between the groups. Next slide. And for mepolizumab in two trials and 437 participants, mild adverse effects were common, and there were no differences found between groups. Next slide. And now, we are going to take a moment to talk about the ongoing studies. Next slide. There are currently two CSU studies that are focused on dupilumab with sample sizes of 72 and 234. They have a shared outcome of the weekly urticaria activity score. There are three ongoing studies for CRS without nasal polyps. And this is interesting because there were not previously any studies including participants with CRS without nasal polyps that were specifically designated as such. The sample size ranges from 30 to 240, and the shared outcomes include that SNOT-22 and the University of Pittsburgh Smell Identification Test. Next slide. There are two trials currently ongoing for CRS with nasal polyps. One is looking at dupilumab with a sample size of 36, and they are also looking at that SNOT-22 but also use of systemic corticosteroids and the severity of rhinosinusitis. And there is one trial looking at mepolizumab. The sample size is 160. And those key outcomes include the total endoscopic nasal polyp score, the nasal obstruction visual analog scale, and that SNOT-22. Next slide. We identified several randomized controlled trials that evaluated omalizumab, dupilumab, and mepolizumab for the indications of interest. There were no available head-to-head trials. Instead,

all of the identified trials compared the subject medication to placebo. The certainty of the evidence for relevant outcomes was generally rated as moderate, and there were no new concerns noted with regard to adverse effects. For CSU, specifically, we found that omalizumab 300 mg administered every four weeks consistently achieved significant differences in the assessed outcomes. Future studies assessing increased doses may be beneficial. Next slide. For EGPA, the research was scarce, resulting in a low certainty of evidence for efficacy outcomes. The data suggest that mepolizumab 300 mg administered every four weeks could be utilized to decrease relapse and sustain remission. Given the progressive nature of this condition and the potential for severe outcomes up to and including death. This is a valuable finding. Additional evaluations of symptom relief, use of systemic corticosteroids, and quality of life would be beneficial. For HES, the administration of mepolizumab resulted in a reduction in systemic steroid use and reduced flare occurrence. Similar to EGPA, this condition can result in serious health outcomes, so the finding that mepolizumab can do decrease flares is significant. Next slide. All three of the biologics of interest demonstrated the efficacy in improving both symptoms and quality of life in participants with CRS. Dupilumab demonstrated inconsistent improvement in the FEV1, though there were few studies assessing this endpoint, and there were no studies that assessed this endpoint as the primary outcome. The majority of the identified studies included only participants with CRS with nasal polyps, and none of the identified studies assessed CRS without nasal polyps, specifically. In CRS with nasal polyps, all three biologics were shown to decrease nasal polyp burden as evidenced by the nasal polyp score as well as the nasal congestion score. Next slide. So this concludes this presentation. And I just want to thank you for your time today. And I would be happy to answer any questions that you have about this review.

Jordan Storhaug: Thank you, Courtney. Just we could double-check. I am not seeing any questions. Thank you so much. With that then we will move on to our stakeholder input. For each of these, there will be three minutes available for comments. And our first one is Margaret Olmon of AbbVie.

Margaret Olmon: Hi, can you hear me?

Jordan Storhaug: We can hear you.

Margaret Olmon: I am on the atopic dermatitis presentation instead of this one. **[cross-talk]**

Jordan Storhaug: Oh, I am sorry **[cross-talk]**. Catch me up here. I lost myself. So. Yeah.

Margaret Olmon: That's okay. I will talk to you soon. Thanks.

Jordan Storhaug: We will see you after that one. So my mistake there. Actually, our first and only one here is Long Nguyen of GlaxoSmithKline.

Leta Evaskus: Okay, **[cross-talk]** this is. Oh, I'm sorry. Go ahead.

Long Nguyen: Yes, good morning, everybody. And my name is Long Nguyen. I am a Health Outcome Liaison from Medical Affairs at GlaxoSmithKline, providing comments on Nucala. And I would like to extend my appreciation for wonderful clear evidence demonstrated from Dr. Gamston based on the DERP report very accurately. And thank you so much for your work on that. I just want to make a couple of comments to remind the committee that in addition to severe asthma, Nucala is the only biologic indicated to treat rare eosinophilic driven disease such as EGPA or, as you already know, Churg-Strauss syndrome, as well as HES. And as Dr. Gamston alluded to, these severe diseases do have very negative consequences in patients who are diagnosed with them. It could result in death but also result in significant changes and detrimental changes in quality of life. I just want to remind the committee that in all clinical trials in patients diagnosed with EGPA, our trials show that adding Nucala to standard therapy of daily OCS and immunosuppressive, so these patients were not on placebo. They were on standard of care, and the patients receiving Nucala sustained a duration of remission and reduced the daily average of doses of oral corticosteroid needs compared to those who receive standard of care. And similarly in the hypereosinophilic trial, or HES, Nucala statistically significantly reduced the annualized rate of flares by up to 66% in patients diagnosed with HES. So since Nucala is the only biologic indicator for these two rare diseases and is currently not referred on the PDL, I asked the Committee to vote to have Nucala available as a preferred biologic for patients diagnosed with EGPA and HES on the Washington PDL drug list. And so thank you very much. That will conclude my comment for today, and I will be happy to take any questions. You are on mute.

Leta Evaskus: Jordan, you are on mute.

Jordan Storhaug: Thank you. So thank you so much for that presentation. I just wanted to give an opportunity for people as well if anybody wants to raise their hand to speak. **[cross-talk]**

Leta Evaskus: Yeah. This is Leta. I don't see any hands raised.

Jordan Storhaug: So let's go ahead and take a look at the motion.

Leta Evaskus: Me one second to get that up.

Kavita Chawla: Kavita Chawla here. So Leta or Donna, just for clarification, is our motion going to be the motion as listed there except just the three drugs that were reviewed today? Not including the benralizumab and the reslizumab?

Donna Sullivan: No. This is Donna, it would include all of the drugs. That was just an add-on from the previous reports.

Kavita Chawla: Okay.

Leta Evaskus: This is Leta Evaskus. Ryan Pistoressi, maybe you can talk to us a little bit. So these are biologics for non-asthma conditions, so the end of this would have to be changed.

Ryan Pistoressi: Right. And I guess maybe what we can do is carry these drugs forward so that way they are not lost and just kind of focused on the details for what was reviewed in today's report and for those conditions. So this was for the non-asthma conditions, but we will still be able to carry this forward since these are the biologic drugs for asthma.

Leta Evaskus: So this is Leta. Maybe I will just start this off op here for non-asthma. And do I include chronic spontaneous urticaria or leave that off?

Donna Sullivan: This is Donna. I believe if we just delete asthma from the motion. Did we cover those other indications? The chronic spontaneous urticaria and other indications?

Ryan Pistoressi: Yeah, we might want to say they are FDA-approved indications.

Donna Sullivan: Yeah, because we looked at the rhinosinusitis, urticaria, eosinophilic granulomatosis, hypereosinophilic syndrome, and nasal polyps.

Ryan Pistoressi: Right. Yeah, instead of listing them all just for the treatment of their FDA-approved indications for non-asthma. I am not sure what the **[cross-talk]**.

Donna Sullivan: Why don't you say their FDA indications exclude asthma?

Ryan Pistoressi: Yeah, okay. That works **[cross-talk]**.

Donna Sullivan: And Kavita, this is Donna again, going back to what you said. I forgot that this was the non-asthma biologics and then we are doing it differently. So yes, we would only be speaking to the three drugs that were reviewed today. The other drugs will be reviewed for their asthma indications separately.

Susan Flatebo: This is Susan Flatebo. After considering the evidence of safety, efficacy, and special populations for the treatment of chronic spontaneous urticaria and FDA-approved indications excluding asthma, I move that dupilumab, mepolizumab, omalizumab are safe and efficacious for the treatment of their approved indications. Dupilumab, mepolizumab, and omalizumab can be subject to therapeutic interchange in the Washington PDL for chronic spontaneous urticaria and the FDA-approved indications excluding asthma. Was that right?

Donna Sullivan: Yeah, Leta was going not as fast. This is Donna. As a friendly amendment, I think we could delete spontaneous urticaria and just say their FDA-approved indications excluding asthma. It will be a little bit less awkward.

Susan Flatebo: Does that make sense up here too for the treatments that are FDA-approved?

Donna Sullivan: Yes. [cross-talk].

Kavita Chawla: This is Kavita Chawla. I second the motion.

Jordan Storhaug: All right, then. All in favor, please say "Aye."

Multiple speakers: Aye. Aye. Aye. Aye. Aye.

Jordan Storhaug: Any opposed? All right. It looks like we can pass unanimously.

Laura Beste: This is Laura Beste. I just had a quick question. Since the previous recommendation from 2021 refers to chronic spontaneous urticaria, does

this automatically replace that because it lists it separately? So until the asthma one is reviewed again, it would override it?

Ryan Pistoressi: This is Ryan. That was the motion from 2021 before this report. It kind of split off and was focusing on all these other indications. So I wouldn't necessarily say that we would need to re-review the asthma ones to update that. I think the previous drugs that were reviewed and have that motion would still apply going forward. It is just that this new one that we reviewed and approved just now would be able to apply going forward on top of that. So it would be in addition to the chronic spontaneous urticaria that was mentioned in that last motion.

Laura Beste: Okay.

Jordan Storhaug: Okay, any other questions on that topic? Now that our schedule is kind of modified there, I am hoping we are able to try to do atopic dermatitis now and get that report from Wesley Lindsey.

Wesley Lindsey: I have been warming up on the sidelines over here, so I am ready to get in the game whenever you would like, Coach.

Leta Evaskus: Thank you. This is Leta. I am opening up the presentation now.

Wesley Lindsey: Do you prefer a camera on, camera off for the presenter? Camera on would be great. Oh, good. I will put a tie on today. So that hasn't happened in some time, probably.

Leta Evaskus: Sorry, my computer is taking a minute here to open this.

Wesley Lindsey: No, this is fine. And while we are transitioning into this, I am not sure if my affiliation is completely clear. I am presenting from Auburn University today. So I understand in Spokane you also have a basketball team, Gorgonzola, or something like that, that seems to think they are pretty good. But we're coming. We are getting better at this. Yeah. Is that not what it is called? Did I get the name right? I don't know. Jordan?

Jordan Storhaug: Something like that **[inaudible – crosstalk]** bit later, maybe.

Wesley Lindsey: Okay. I will say we are new to this good at basketball thing, so our trash talk is probably not as good as it needs to be. It is still a work in progress.

Jordan Storhaug: All right.

Wesley Lindsey: So you'll have to help us out on that. Sounds very good.

Jordan Storhaug: All right. I think we are all set, so you can start whenever you are ready.

Wesley Lindsey: All right, thank you very much. I really am glad to join you today. I do always enjoy getting out and getting to present to some new folks. And it's my pleasure today to talk about atopic dermatitis. So next slide, please. So this has been an area that has had a lot of activity, and I know that you know that because this is why we are talking about it. There have been quite a few new drugs, a lot of new developments in this particular therapeutic area. For our overview, we follow the typical DERP process for a systematic review, and we will have all the traditional components that you have come to expect as part of a DERP review. And we had a previous systematic review on this topic done, which we will talk about in just a moment. So next slide, please. A little bit of background and context. Atopic dermatitis is something that we are probably all on the call familiar with. It is a chronic inflammatory skin disease. It can cause intense itching and recurrent lesions that relapse and remit. It can be caused by environmental, genetic, and immunologic components. Usually, it shows up or presents by age 5, but it still can manifest later and present later in life. Adults and children report atopic dermatitis negatively impacting their self-esteem, reporting limiting social interactions. Also, they talk about they avoid discussing their condition, and it also has a strong impact on their clothing choices, that they typically want to cover up and may not be able to dress in the manner that they would like to do. The initial treatments typically start with avoiding triggers if we have some known trigger that causes that. If we are not able to control disease, we move along to something like using moisturizers, potentially corticosteroids, and also incorporating phototherapy, if needed. So, next slide. As I mentioned, this is an update to a previous DERP Systematic Review from 2017. And in the previous report from 2017, we identified 43 randomized controlled trials from the listed interventions. What you will find, though, is a preview of coming attractions for a little bit later in the report. There wasn't a whole lot that we were able to carry forward from this 2017 report to today, and a lot of that was because the 2017 report focused on mild to moderate atopic dermatitis, whereas you will see in just a moment when we get to the PICOs for this report, we focused on moderate to severe. Also, the comparators that were assessed in the previous report in 2017, that was a

little bit different than the comparator structure for what we wanted to evaluate for this. So even though that was a very good report, it is a little bit different from what we are going to be talking about today, just in terms of severity and the agents that are involved. So next slide, please. The populations that we are going to look at: We are going to look at adults and children. So essentially all ages with moderate to severe atopic dermatitis. Next slide, please. As I mentioned, this is a therapeutic area with a lot of activity. So what you are going to see on this particular slide, these are the FDA-approved agents, but we will classify these as maybe the older FDA-approved agents. So these are all the agents that were approved in 2017, prior. And a lot of these names are going to look familiar to you. You can see that we have quite a few different drug classes from immunosuppressants to calcineurin inhibitors, etc., and so these are the older agents that we are going to use. I am also going to just go ahead and throw a disclaimer out there talking about pimecrolimus and tacrolimus. There is a lot of confidence in people in how they say these, but nobody is exactly sure. So how I pronounce them later on in the presentation it may just be whatever the moment strikes me. So that is part of the fun is being able to pronounce these different ways. And, hey, confidence over competence sometimes when it comes to pronouncing drug names. So just a little bit of a warning there. Plus, if I pronounce it differently every time, I never have to remember, "How did I say it last time?" and try to be consistent. So I will just go ahead and throw that out there for everybody's benefit. All right. Next slide, please. So this is the newer set of agents. So these have all been approved from September 2021 to the present. As you can see, two of those were approved in January of 2022. So we have three Janus kinase inhibitors and the one interleukin-13 antagonist that have all again been recently approved for atopic dermatitis. And actually, when we started the project, all four of these were still considered pipeline agents but, again, now have all made it to market and been FDA-approved. Next slide, please. So this is the final list of agents that we will be talking about. These currently are still in the pipeline working towards FDA approval for atopic dermatitis. So you can see our baricitinib, lebrikizumab, nemolizumab, and tradipitant. So those are the four agents currently still in pipeline status, and we will, again, be talking about those a little bit later in the presentation. So next slide, please. The comparators, so we want to look at any of the other included interventions, so anything that we can evaluate head-to-head. We wanted to evaluate with top with or against topical corticosteroids, and also for the pipeline therapies we wanted to look at standard of care or placebo. Next slide, please. For the outcomes, we wanted to look at a number of efficacy and effectiveness outcomes. These

are the ones that we are going to focus on for our presentation today, the Investigator Global Assessment (IGA), the Eczema Area and Severity Index (EASI), the Scoring Atopic Dermatitis, which is our SCORAD, and then we had two different quality of life assessments, the Dermatologic Life Quality Index, which is used in adults, and the Children's Dermatology Life Quality Index, which is used in children. And unfortunately, I don't have any great acronyms like Dr. Gamston had in a previous presentation where one of her assessment tools is called the SNOT. Unfortunately, mine is just a little bit less colorful than that. So for our next slide, we will talk about our harm outcomes, and traditional harm outcomes, overall adverse events, serious adverse events, and then withdrawal of treatment due to adverse events. For our study designs, we focused on randomized controlled trials for this specific review. Alright, next slide, please. Our key questions would be those that you would traditionally expect with a DERP systematic review, we want to look at the comparative effectiveness of the FDA-approved interventions as well as the comparative efficacy of the pipeline therapies. Look at the comparative harms of those, and then look at the characteristics of ongoing studies for the interventions that are included in this review. Next slide, please. So to get into our methods, next slide. We followed the traditional DERP Systematic Review Process. We evaluated the typical DERP evidence sources such as Medline, Cochrane Library, Google Scholar, etc., and the traditional ongoing studies sources such as clinical trials and the FDA. And then we also use the resources that were explored in the previous report from 2017, and we evaluated the randomized controlled trials and meta-analyses as well as there were also some additional systematic reviews, and we evaluated the bibliographies, etc., for any additional and relevant resources or studies for this project. Our next slide. Again, following our traditional DERP stepwise methods, we searched our evidence sources, performed our distiller screening and evaluation of those at the risk of bias assessments, used our great approach for certainty of evidence and then searched the resources mentioned for our ongoing studies. Next slide, please. So this is the again typical DERP Risk of Bias Assessment. The levels and the descriptions are the same. The color codings have changed just a little bit. So in Courtney's presentation, previously, you saw we sort of had the red/yellow/green color scheme. And now we've changed that a little bit. So you can see that low is represented as this sort of light blue color, moderate is sort of the purple color, and then those that had a high risk of bias are indicated with red. Next slide, please. Similarly, the color system for the Grade Certainties of Evidence has been adjusted a little bit. Again, the descriptions are the same. And for this particular report, I mentioned earlier, the clinical assessments that we

used for our grade rating, which are the SCORAD, EASI, IGA, and the Quality of Life Assessments as well as the adverse events. So as you can see, again, those that have a high certainty of evidence will be indicated with this light blue color. Outcomes associated with a moderate color, or a moderate level of evidence associated with this purple color. A low certainty of evidence will be this orange color, and then a very low will be this a more bright reddish color. Next slide, please. So what we are all here for, let's dive into the findings for our atopic dermatitis medications. So next slide, please. These are just very brief descriptions. I am not going to go through all of this with you but just wanted to provide a brief overview of the outcomes that are being used for the grade assessment for this review. So you can see again, just a brief description here of the life quality indices, the eczema area and severity index, the IGA, and the SCORAD. So you can see that they all have slightly different scales and levels from 0 to 30, 0 to 72, 0 to 4, etc. And one thing that I do want to just kind of take away from this is for all of this assessment higher scores indicate more serious or more disease activity. So as we talk a little bit later in the slides, for all of these we are looking to lower the scores for all of these assessments. And I know that is not always the case for every therapeutic area, but for this one, high scores commonly indicate worse disease, low scores indicate improvement. So our next slide, please. So here is our Prisma diagram to give you an indication of the flow of information through our project. And if you just want to hit the next advance, I think it will highlight the bottom portion of our Prisma diagram. There you go. So you can see we started with 174 documents through our searches and 66 in the original report that included randomized controlled trials and other resources. And eventually, we worked our way down to 47 original publications for this review, and six which we carried forward from the previous 2017 DERP review. So a total of 53 publications. And as you can see on the next slide, we had 47 original publications as I just mentioned, and 40 of those were original studies. You can see the list below there. These are the sort of tally of studies that we had for all of the FDA-approved therapies. So you can see them listed alphabetically. You can see that cyclosporin had the largest number of studies. And one thing that I will also point out with the sub-bullets to cyclosporine, is it also had several head-to-head comparisons, which we will talk about in just a moment, as well, with other active therapies for atopic dermatitis. As noted in the bottom for crisaborole, dupilumab, and tacrolimus we had no new studies for this particular review that we were able to find that fit within the scope of our project. Next slide, please. So this is what we found for the FDA pipeline therapies. So you can see for baricitinib, six studies, lebrikizumab two, nemolizumab three, and for

tradipitant, we did not find any studies published at that time that we initiated this project for atopic dermatitis. So there are quite a few that are going on and in process, but none have been published at that project initiation. Next slide, please. All right. So here is kind of the star of the show, this and the next three slides. So what we have for this particular slide, these are those older agents that we have. So the azathioprine, cyclosporine, omalizumab, pimecrolimus. And so these are the previous 2017 and prior approved FDA or FDA-approved products for atopic dermatitis. So on the left, you can see the comparator that is being evaluated. Across the top, you can see the assessment tool or the assessment that we provided a grade outcome for. And then in the body of the table, you can see the assessment of the grade certainty of evidence that was assigned to each of these particular therapies and to the intended outcomes with it. So generalizing as we look through the table, you can see that for azathioprine, many of the outcomes that were assessed in this case were assessed as low. For cyclosporine, virtually all of the outcomes that we graded for this particular therapy were assessed as very low. For omalizumab, again, it is that orange color, and you can see that those are assessed as low. And with pimecrolimus, you can see that we had moderate certainty of evidence with that particular intervention. So just kind of generally speaking in the big takeaway, you can see that for those older therapies the certainty of evidence is not particularly great for those treatments. So if we can move to the next slide, please. So this is the same information, but this is for the batch of newer agents, so the ones that have been approved in the previous six months. Once again, you can see on the left-hand side the agent and the comparator that is being evaluated. Across the top is the assessment that is being graded. And within the body of the table, you can see the grade and actual certainty of evidence that was assigned to that particular comparison and outcome. So you can see with abrocitinib versus placebo, for the certainty of evidence we evaluated that as being high. For abrocitinib and dupilumab and placebo, mostly moderate level of evidence there. Ruxolitinib had a high level of evidence. Tralokinumab was a little bit different. We had moderate to low. We saw some inconsistencies, and we will talk about some of those specific studies which led to our sort of downgrading of evidence for this particular agent, and for upadacitinib generally having high certainty of evidence for these studies. If we can move to our next slide. So this is the certainty of evidence that we assessed for the pipeline therapies. So you can see baricitinib, lebrikizumab, nemolizumab. For baricitinib, we generally assess it as having a high certainty of evidence. For lebrikizumab and nemolizumab, we see a bit more inconsistency. And as you will see a little bit later on, we will again

describe in a little more detail than what we saw was inconsistent outcomes and maybe even some overlap in indirect comparisons of studies between placebo and these active treatments. And so, again, maybe not as a consistent change as you might see for some of the other therapies. So those are some of the sorts of big picture takeaways and visuals for this. And if we can move on to our next slide. We will talk about just a few specifics of how much clinical change or how much change that we saw on the assessment tools for each of these individual comparators. So if you will move to the next slide. So I will just take one moment to orient you to the slide. So the top of the slide indicates the medication and the comparator. You can see within the green the number of clinical trials. And then the risk of bias associated that was assigned to the clinical trials as part of that. And then the grade assessment. And then you can see some of the specific outcomes that we want to talk about. So I wanted to orient you to this slide because the next 100 to 106 slides or so are all structured the same way. So I want you to be familiar with that. I am just kidding. We don't have that many slides. I know. All right. For abrocitinib and placebo, we had four randomized control trials. We wanted to show that it did show that it was more efficacious than placebo in adults for IGA and for the outcome of EASI-75. And so what the EASI-75 is at least 75% improvement from the EASI score from baseline. So for IGA of 0 or 1, which indicates no disease or minimally active disease at 12 weeks [indistinct] abrocitinib, you could see 38 to 44% of participants achieved an IGA of 1 or 2 for placebo that was 5.8% to 9%. For EASI-75, again, that is a 75% improvement at 12 weeks for abrocitinib. You can see almost two-thirds of participants achieve that goal, whereas 10% to 15% of participants in the placebo groups. So our next slide, please. Here we have abrocitinib versus dupilumab, as well as there was a placebo arm in this study. There was only one randomized controlled trial that had this comparison set. You can see again for the IGA of 0 or 1. For abrocitinib, roughly 50% of participants achieved that particular therapeutic goal; just over a third of participants for dupilumab; and 14% of participants for placebo. And for EASI-75 again, abrocitinib almost half of the participants there; dupilumab again just over a third of participants; and then placebo nearly 13% achieved that EASI-75 at 16 weeks. Our next slide. So one of our older agents, azathioprine versus methotrexate. And so for this particular agent, you can see that the grade was assessed as low, and that reflects back into that color table that was a little bit earlier. We saw that azathioprine was equally as efficacious as methotrexate when it comes to SCORAD and IGA assessments over 12 weeks. And listed there are some of the SCORAD, and this had long-term follow-up data. For SCORAD at 12 weeks, we saw a drop of

approximately 22.5 points in each group. And in the SCORAD at five years, we saw a 32-point drop, and that was from a baseline of roughly 55. For azathioprine, we saw similar adverse events reported with that as well as methotrexate: High levels of gastrointestinal side effects, which should not be a surprise, 55%, and 59%, respectively. We also saw high levels of blood count abnormalities, in particular, lowering your impact on white blood cells, and 77% of participants in the azathioprine groups reported changes in white blood cells. So next slide, please. For azathioprine versus placebo. We saw that azathioprine was more efficacious than placebo up to five years. One of the things that was noted was improvements in sleep disturbances and work disruption. That was specifically indicated, and that was statistically significant. Azathioprine, as no surprise, reported higher adverse events than placebo, with a high level of gastrointestinal effects. And with this, we also saw again high levels of lymphopenia with azathioprine; 43% of participants had a drop in white blood cell counts on azathioprine therapy. Next slide, please. Another one of our more classic agents with cyclosporine versus methotrexate. This one the grade was very low. Cyclosporine was superior to methotrexate as assessed by SCORAD-50. Similar to EASI-75, a SCORAD-50 indicates at least 50% improvement in the SCORAD from baseline. For cyclosporine, we saw 42% of participants achieve a SCORAD-50 at week eight, whereas for methotrexate only 80% of those achieved that particular therapeutic goal of a SCORAD-50. Cyclosporine was similar to methotrexate in pediatric patients on SCORAD at week 12. So you can see with cyclosporine and methotrexate similar reductions in SCORAD in pediatric patients. Next slide, please. For cyclosporine versus mycophenolate. One randomized controlled trial, and this had a grade of very low. We saw similar efficacy of cyclosporine and mycophenolate over 48 weeks. One sort of therapeutic note was participants noted slightly quicker onset with cyclosporine, and SCORAD was changed approximately 20 points in both treatment groups. So as you can see, maybe from some of the previous data that we presented, a 20-point reduction maybe is in line or maybe even a little on the lower side for some of those previous therapies mentioned. Participants reported less prednisone use with cyclosporine, so they needed less rescue corticosteroids, but there were some notable adverse events with cyclosporine compared to mycophenolate including anemia and excessive hair growth in patients. Next slide, please. For cyclosporin versus placebo. We saw that cyclosporine was more efficacious than placebo. But the assessment tools used were ones that were more that were previously used and maybe not used as commonly or reported as commonly anymore, such as the Rule of Nines Area Assessment. High rates of adverse events were

reported in the cyclosporine group of 12 to 23, and more discontinuations occurred in the placebo groups due to lack of efficacy. So that can make it sometimes a difficult assessment or a difficult comparison to make if we see high discontinuation rates in one group compared to another. Next slide, please. So cyclosporine versus prednisolone. So we saw an initial response that was about the same between the two groups. But cyclosporine did report superior efficacy in the measure of stable remission, so that was over a longer period of time. This study was ended early after a pre-planned analysis because we saw cyclosporine being more efficacious over that stable remission phase. And patients and/or the participants in the cyclosporine group reported higher rates of common cold, skin infections, and loss of skin sensation. Next slide, please. So cyclosporine versus tacrolimus. So we had one randomized controlled trial that made this head-to-head comparison. So tacrolimus was more efficacious and cyclosporine during the first five weeks of treatment. And you can see the change in the SCORAD score of minus 52 points and minus 57 points, but after six weeks of treatment, this change was no longer significant, and both of them demonstrated similar efficacy through the rest of the study. And there were very few adverse events reported, only four in each group of 15. You can see that this was a very small study, and thus probably part of why this had a very low grade on certainty of evidence. Next slide, please. So for omalizumab versus placebo, we saw that omalizumab was more efficacious than placebo at 24 weeks, however, it didn't achieve the minimum clinically important difference that was established in the study of minus 8.7 points, and the actual difference that was achieved was minus 8.3 points. And I wanted to pause on this and really emphasize that of all the studies, the 40 new studies that we found, this is the only one that listed a minimum clinically important difference established by the investigators. So this is at least somewhat notable as a takeaway for us today. The Quality of Life Assessment was superior, and it was improved more or beyond the minimum clinically important difference that was defined by investigators in this case, so they did achieve a therapeutic goal. So worsening of atopic dermatitis was noted as an adverse event, and so we saw high total reports in both of those groups. And for gastrointestinal issues, you can see roughly 20% of participants reported that in both the omalizumab and the placebo groups. Next slide, please. For pimecrolimus and topical corticosteroids. This study enrolled infants from 3 to 12 months. Both groups saw a rapid improvement and are reporting success as defined as an IGA of 0 or 1 by week three. Nearly half of participants in both groups reported that treatment success. This is a five-year follow-up study. So at the end of the five years, nearly 90% of all treated participants in both groups

achieved that IGA assessment of 0 or 1. One of the items that they did assess was topical corticosteroid use. And so participants in the pimecrolimus group used the product a median of 224 days over the five years. And so in the other, they used the topical corticosteroids, any topical corticosteroid comparator group a median of 178 days. So common adverse events that were reported are nasopharyngitis, fever, and bronchitis. Next slide, please. One of our newer agents, ruxolitinib versus placebo. So ruxolitinib was superior to placebo based on EASI-75. At eight weeks, you can see 51% to 78% of participants achieved that EASI-75. And in the placebo groups, roughly 25% of participants achieved an EASI-75. Participants in ruxolitinib were also more likely to achieve an IGA of 0 or 1. And you can see that in the two studies that we had, one of those the odds ratio is the likelihood to achieve an IGA of 0 or 1 was 7.5, and in the other, the odds ratio was 15.8. And you can see the attendant confidence intervals associated with that. Next slide, please. For tralokinumab, which again is one of our newer kids on the block. So we had four randomized controlled trials. Study periods were up to 52 weeks, and we had a relatively large participant pool of almost 2200 unique participants. So tralokinumab 300 mg showed significant inconsistent results. So for an EASI of 75, you can see that for tralokinumab anywhere from 25% to 56% of participants achieved that therapeutic goal, whereas, in placebo, 11.5% or 11.4% to 35.7% of participants achieved an EASI of 75. So you can see that for some of the studies the lower end of the tralokinumab effectiveness in the higher end for placebo response overlap a bit. So that is what we mean when we say inconsistent results. Quality of Life was assessed with a Dermatological Life Quality Index that was significantly improved at 12 weeks, and you can see the effectiveness there. Placebo a 3-point improvement with tralokinumab and almost 7-point improvement from about a 13-point baseline. Next slide, please. All right, these are in alphabetical order. So we are in the U's, so we are almost there. Hang in it. So for upadacitinib versus dupilumab, we see superior efficacy of upadacitinib in achieving an EASI of 75 at week 16. For upadacitinib, we see a 71% response rate for dupilumab, a 61% response rate. So that is a relatively high response rate for upadacitinib. And more participants reported hepatic disorders and elevated creatine phosphokinase in the upadacitinib group compared to dupilumab. Next slide. Alright. Upadacitinib and placebo. So we see that upadacitinib was superior to placebo for both EASI and IGA. For upadacitinib, 52% to 62% of participants achieved an IGA of 0 or 1, and for placebo, roughly 5% to 10% of participants. For EASI-75, upadacitinib 73% to nearly 80% response and placebo 13% to 26% response. So a relatively high response rate for upadacitinib both in this one and in the study that was

mentioned in the previous slide. Next slide, please. Alright. So we have made it through our FDA-approved therapies. Let's take a look at the findings for our pipeline therapies. Next slide, please. So for baricitinib and placebo, we see that baricitinib was superior to placebo, again, as IGA and EASI of 75, you can see with IGA of 0 or 1. For baricitinib, almost 17% to 31% of participants achieved that therapeutic goal as opposed to placebo 5% to 15%. So, overall, for IGA 0 or 1, you can see a lower overall response rate doing an indirect comparison than maybe with some of the others that we have talked about today. And same with EASI-75 for baricitinib, 25% to 48% of participants achieved that therapeutic goal, and in placebo almost 9% to 23% of participants. So this did include a 68-week extension study. So we have longer data for baricitinib than a lot of the newer agents that we have talked about. And discontinuation rates were similar between baricitinib and placebo. Next slide, please. For lebrikizumab and placebo, we had two randomized controlled trials for this. We can see that lebrikizumab was superior to placebo again by IGA and EASI. And that has been one nice feature for the newer agents is to at least see consistent outcomes reported so that you can make those indirect comparisons. So for an IGA of 0 or 1 for lebrikizumab, you can see roughly a third to a half of the participants there achieved that IGA goal, and for placebo, 15% to almost 20% of participants. For EASI-75, lebrikizumab roughly 60%, and then for placebo 24% to almost 30% of participants achieved that goal. So high-risk placebo response rates in these groups of participants. Quality of Life, however, was not consistently improved compared to placebo. And that was one of the elements that you can refer back to the grade table that we had earlier in the presentation why this would lead to a downgrading on the certainty of evidence because of that inconsistency. And adverse events such as injection site reactions were mild to moderate and similar to placebo. Next slide, please. For nemolizumab, we had three randomized controlled trials. Once again, we see that it was superior to placebo in IGA and EASI. For IGA of 0 or 1, the nemolizumab, roughly a third of participants there experienced that therapeutic goal, whereas with placebo 7% to 21%. And we see there, P is variable within studies, so some studies demonstrated statistically significant differences, and some did not. And that is what that means by P variable. And the same for the EASI of 75. We see for nemolizumab 45% to 50% of participants responded with an EASI of 75, placebo 16% to 25%. Once again, that did not achieve statistical significance in all of the studies that were published. The Quality of life compared to placebo was improved. Next slide, please. Alright. So the findings for our ongoing studies. Next slide. So for our ongoing studies, we identified 32 ongoing studies. You can see for our FDA-approved

therapies we have abrocitinib with four, crisaborole - two, dupilumab - four, ruxolitinib - one, tralokinumab - four, and upadacitinib - two studies. For the pipeline therapies, which is on our next slide, we can see that for baricitinib - four studies, lebrikizumab - five, nemolizumab - four, and tradipitant, they have two ongoing studies. Sample sizes range from 228 to almost 1800 participants. And nemolizumab has a small substrate study in progress to assess for drug interactions. Alright, next slide. To our discussion. So next slide, please. The way that we framed this discussion, we wanted to talk about those that had moderate to high certainty of evidence and kind of group those together. So that doesn't necessarily mean that they are more efficacious but just that the level of evidence for these were a little bit higher. So for abrocitinib, we felt that it was efficacious compared to placebo. For the baricitinib, once again, efficacy outcomes were superior to placebo. But if we did make indirect comparisons, particularly to some of the newer agents, baricitinib seemed to have overall lower response rates. Upadacitinib was superior to placebo and dupilumab and, again, making these indirect comparisons but using common endpoints and relatively common study durations, upadacitinib tended to have higher response rates than some of the other therapies that we evaluated. And as no surprise, the newer agents demonstrated efficacy with larger studies than those older agents that we had. Next slide, please. So those that had low to very low certainty of evidence. Azathioprine did show efficacy but had a lot of adverse events and high discontinuation rates when studied long term. Cyclosporine was also generally efficacious. The studies associated with cyclosporine tended to have a high risk of bias and also a lot of adverse events. Again, that lymphopenia was something to be noted with cyclosporine. Lebrikizumab was superior to placebo, but generally speaking, effect sizes were relatively small compared to some of the other particularly newer agents. And nemolizumab showed inconsistent results in efficacy study to study, not all of those achieving statistical significance. Omalizumab was superior to placebo, but it did not meet that minimally clinically important difference that was defined by investigators at 24 weeks. And omalizumab and pimecrolimus have long-term study data up to five years, in which 90% of participants treated showed treatment success. And next slide. I would be happy to take any questions that you have. Jordan Storhaug: Thank you, Wesley. I really appreciate it on the flexibility today as well. With that, I think we are ready to go on to our stakeholders. I will remind anybody if they are not one of the three that are pre-registered, they can raise their hands and we will get to them. But I already was excited to get connected with our first stakeholder, which was Margaret Olmon of AbbVie.

Margaret Olmon: Okay, I think I am unmuted. Can you hear me?

Jordan Storhaug: I can hear you. Thank you, very good.

Margaret Olmon: All right. Well, first, I would like to thank Dr. Lindsey for that exceptional report. This is a lot of information going on in the atopic dermatitis. My name is Dr. Margaret Olmon with Medical Affairs at AbbVie. I want to thank you so much for allowing me a few minutes to provide information on upadacitinib with the brand name Rinvoq. My focus will be on the newest indication. Rinvoq has been FDA-approved to treat patients 12 years and older with refractory moderate to severe atopic dermatitis not adequately controlled with other systemic medications or when the use of those therapies is inadvisable. Treatment should be initiated with 15 mg taken orally once daily. If an adequate response is not achieved, providers should consider increasing the dose to 30 mg a day. Atopic dermatitis is the most common and most severe type have eczema and is characterized by itchy and inflamed skin. Providers and patients with moderate to severe AD are looking for treatment that will offer rapid reduction in itch and pain along with the lessening of inflammation, redness, and thickening of the skin. Rinvoq has differentiated itself from other medications currently available for the treatment of atopic dermatitis. Rinvoq at both 15 mg and 30 mg daily doses met all primary and ranked secondary endpoints in three pivotal trials. Measure up 1 and 2 looked at monotherapy treatment, and AD Up was a trial that evaluated Rinvoq in a combination with topical corticosteroids. In these studies, the investigators noted a rapid onset of action. Over two-thirds of patients saw a statistically significant 75% improvement in skin symptoms after 16 weeks and a significant reduction in itch was seen as early as day two with Rinvoq 30 mg and day three with 15 mg. In all three studies, Rinvoq demonstrated disease control for adults and adolescents through the double-blind placebo period and with and without use of topical corticosteroids. Rinvoq has a well-studied clinical profile with over 7500 patients studied in rheumatoid arthritis and psoriatic arthritis and now with over 3200 additional patients in the AD Phase 3 program. The safety in the AD studies was consistent with the previous trials in RA and psoriatic arthritis. This has been only a short review. Please review the prescribing information for full efficacy and safety information online at rxabbvie.com. I want to close by respectfully asking that Rinvoq be added to the state Preferred Drug List for all indications including atopic dermatitis. Thank you for your time and

consideration. I would be happy to answer any questions that you might have at this time.

Jordan Storhaug: Thank you very much. For our next one then is Minh Nguyen, of Pfizer. We have two topics for this one, so it'll be five minutes of time that we are able to give to the stakeholder.

Ming Nguyen: Thank you. I am just checking to see if you can hear me.

Jordan Storhaug: We can hear you. Thank you.

Ming Nguyen: Yep, fantastic. I believe it is technically still the morning, so good morning to the Committee Members. My name is Ming Nguyen. I am one of the Field Medical Directors with Pfizer's Dermatology Group. So I am here today to provide a medical presentation on two products for atopic dermatitis. So, the first product is you Eucrisa, which is also called crisaborole. It is a topical non-steroidal for the treatment of mild and moderate atopic dermatitis. It is indicated for adults and pediatric patients aged three months and older. The contraindication for Eucrisa is if the patient has a known hypersensitivity to crisaborole or any component of the formulation. The safety and efficacy profile of Eucrisa was established in two double-blind randomized vehicle-controlled studies. Additionally, Eucrisa was studied in a 48-week open-label safety extension study in patients two years of age and older. Safety assessments included adverse events, vital signs, ECGs, clinical lab parameters, and local tolerability. The most common adverse event occurring in greater than or equal to 1% of subjects was application site pain. Additionally, the use of Eucrisa in pediatric patients ages three months to less than two years was supported by data from a 28-day open-label safety and PK trial in 137 subjects. So I would like to ask the committee to consider Pfizer's request to retain Eucrisa on the PDL. So the second drug I would like to present is Cibinqo or abrocitinib. It is a Janus kinase inhibitor or JAK inhibitor, indicated for the treatment of adults with refractory moderate to severe atopic dermatitis, whose disease is not adequately controlled with other systemic drug products, including biologics or when the use of those therapies is inadvisable. Cibinqo is not recommended for use in combination with other JAK inhibitors, biologics, or other immunosuppressants. It is contraindicated in patients taking antiplatelet therapies during the first three months of treatment. Serious infections, mortality, malignancy, MACE, and thrombosis have occurred in a trial involving another JAK inhibitor in RA patients. The recommended dosage is 100 mg orally once daily, and a 200 mg

oral once-daily dose is recommended for those patients who are not responding to the 100 mg dose. It can be used with or without topical corticosteroids. The most common adverse reactions in subjects receiving the 100 mg and 200 mg in the trials included nasal pharyngitis, nausea, headache, herpes simplex, and increased blood CPK. So the efficacy of Cibinqo as monotherapy in any combination with background topical corticosteroids were evaluated in three randomized double-blind placebo-controlled trials in 1600 subjects 12 years of age and older with moderate to severe atopic dermatitis as defined by typical characteristics including the IGA, the EASI, body surface area involvement, and also the Peak Pruritis Numerical Rating Scale. In the two monotherapy and combination trials, the percentage of patients with an IGA score of clear or almost clear on a 5-point scale with a reduction from baseline of 2 points, and a greater than or equal to 75% improvement, and the EASI was statistically higher in both active [indistinct] compared to placebo. The proportion of subjects achieving an itch improvement in the PPNRS. And week two was also higher in subjects treated with Cibinqo compared to placebo in all three trials. So in conclusion, atopic dermatitis continues to have a high unmet medical need and is costly to manage. To further manage this disease, we need alternative agents available. So by adding an orally administered medication, it will offer an additional treatment option for these patients with moderate to severe atopic dermatitis in the Washington Medicaid population. So based on the efficacy and safety of Cibinqo, I ask that you consider adding Cibinqo to the PDL. Thank you to the Committee for your time today. I would be happy to respond to any questions.

Jordan Storhaug: Thank you. Committee, if you have any questions, just let me know. But next up will be Valerie Ng of LEO Pharma.

Valerie Ng: Hi. Can you hear me okay?

Jordan Storhaug: We can hear you. Thank you. Go ahead.

Valerie Ng: Well, good morning, everyone. I am Valerie Ng, Medical Outcomes Liaison at LEO Pharma. Really glad to have this opportunity to be in front of you virtually and share with you information on Adbry. So Adbry (tralokinumab) was approved by the FDA on December 27, 2021. It is a first-in-class human high-affinity monoclonal antibody that specifically neutralizes IL-13 or interleukin 13. IL-13 has been shown to be a key cytokine driving inflammation in atopic dermatitis or AD skin. And this new biologic is

indicated for the treatment of moderate to severe AD in adult patients whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. And Adbry can be used with or without topical corticosteroids. The recommended dosage is an initial dose of 600 mg via subcutaneous injection, followed by 300 mg every other week. Now, a dosage of 300 mg every four weeks or monthly may be considered for patients below 100 kg who achieved clear or almost clear skin after 16 weeks of treatment. Safety and efficacy profile of Adbry has been established in the extra clinical program for adults with moderate to severe AD, and the efficacy was assessed in over 1900 adult patients in the three pivotal trials where Adbry demonstrated superiority over placebo for primary and secondary endpoints of IGA 0 or 1, EASI-75, and worst daily pruritis score at week 16, and Adbry maintained responses at week 32 and week 52. The most common adverse events reported in the pivotal trials were non-serious and mild or moderate in severity. The overall frequency of AEs was comparable across treatment groups and did not increase during prolonged treatment of up to 52 weeks. The most common adverse reactions were upper respiratory tract infections, conjunctivitis, injection site reactions, and eosinophilia. Overall, Adbry represents a new option in the treatment paradigm for moderate to severe AD in adult patients. With the option to provide this maintenance dosing of every four weeks for eligible patients, their chronic disease may be managed with fewer doses. Therefore, we would ask that the Committee consider adding Adbry to the PDL as a preferred product for adult patients suffering from moderate to severe atopic dermatitis who had an inadequate response to topical prescription therapies. Thank you all very much for your time. And are there any questions I can help answer?

Jordan Storhaug: Thank you very much. I will now pass it over to Leta, and we can go to anybody. I think we have one person I can see who would like to present.

Leta Evaskus: Yeah, this is Leta. Brandon Yip. Brandon, you are unmuted. Can you unmute yourself? Brandon, you are unmuted. Brandon, can you unmute yourself? Brandon, if you can enter in the chat if you are having -- oh, you can't unmute? Okay. Do you want to type your question in the chat? You might be double muted on your computer as well as on the team's meeting. Okay, Brandon, you are unmuted on our end.

Brandon Yip: Hello?

Leta Evaskus: Hi.

Brandon Yip: Hello? Oh my goodness. I am so sorry about this. I was trying to unmute and re-mute, and I ended up just hanging up and trying again. I apologize for the technical difficulties. I know that time is valuable. I just wanted to make two really quick comments. Again, my name is Brandon Yip. I am the Medical Managed Care Director with Sanofi Genzyme representing dupilumab. And I just wanted to comment on just some recent information that we have on dupilumab and atopic dermatitis. And thank you, Dr. Lindsey, for a very thorough examination of all the clinical data strength studies and all that. One of the two things I just wanted to add very quickly was the recently released [indistinct] report at the end of 2021. The conclusion of that report stated that dupilumab is associated with favorable long-term cost-effectiveness compared with JAK inhibitors and tralokinumab in adults with moderate to severe AD. They did indirect treatment comparisons, and they conducted that there was insufficient evidence to support the superiority of abrocitinib and upadacitinib over dupilumab. And then the other quick thing I just wanted to add is that we recently completed a one-year real-world evidence study called RELIEVE-AD. It looks at a number of factors, efficacy, and safety. It kind of aligns with the [indistinct] report. We have not seen any additional safety signals with almost five years of experience on the market across multiple indications. And if you guys are interested in seeing that manuscript, I would be happy to provide that. And I think one point that I wanted to bring to the Committee's attention is that it did reaffirm that the very positive adherence and persistence numbers right across a 30-day grace period adherence was about 91%. And patients that discontinued the drug, understanding that atopic dermatitis wax and wanes, when patients experience flares and remissions, patients restarted the drug within the 116 days. So I just wanted to make those two points with some new data that we had for dupilumab in atopic dermatitis. Thank you, guys. And I apologize again for the technical difficulties.

Leta Evaskus: This is Leta Evaskus. I see that Jon MacKay, the Committee Member, has a question for Dr. Lindsey. So Jon if you could turn on your camera and ask your question.

Jon MacKay: Yeah. Dr. Lindsey, I was just wondering from the older agents in terms of the comparisons of the tacrolimus, was that the oral or the topical formulations that were kind of head-to-head comparisons?

Wesley Lindsey: For the tacrolimus, I believe that was the topical formulation, but let me just double-check. I have my studies right here. Very quickly, I can give it a quick reference and double-check on that. Yep, I was right. It was the ointment versus oral cyclosporine.

Jon MacKay: Thank you.

Jordan Storhaug: All right. Well, thank you, everybody. I think we are ready to consider a motion then. Thank you, Leta, for bringing that up.

Susan Flatebo: This is Susan Flatebo. I just have a question. With this drug class, there are topicals, there are oral agents, there are injectables. How are they preferred? I mean, do they have to fail another topical agent before they can go to oral? I mean, how does that determine which are preferred based on their route?

Donna Sullivan: Hi, Susan. This is Donna. We have clinical policies along these where we typically make them try some of the older topical agents before we move on to the more systemic agents before they try like the monoclonal antibody type agents. So for instance, Dupixent, they have to try, I think, a steroid and either tacrolimus or pimecrolimus before they can get to dupilumab.

Susan Flatebo: Okay, thank you.

Donna Sullivan: And they are in different drug classes, which is why we have a clinical policy. It is not a tried and failed. They are all in different drug classes on the PDL, I believe. At least for the Medicaid PDL.

Ryan Pistoressi: Hey, this is Ryan [cross-talk]. I was going to say, yeah, the same for UMP. So we do have our clinical policies posted online that would go into more detail, but we would have to find them individually and then look through them. So it is really dependent on their drug subclass rather than looking at this kind of disease state as a whole.

Susan Flatebo: And this is Susan again. Yeah, and then plus some of the adverse events related to, cyclosporine, for example. I don't know how that factors in; if that is even something they have to try and fail. I would hope not based on side effects. I mean, how does that even factor in the cyclosporin use? Is that considered preferred? I guess my question is, would they have to fail cyclosporine before they could try another agent in this class?

Donna Sullivan: Hi, Susan. This is Donna again. For Medicaid, the answer is no. We don't consider cyclosporine. We are considering that more of an immunosuppressive agent rather than atopic dermatitis. So it is not required in the Medicaid program as a drug to get to some of the other medications.

Susan Flatebo: Thank you.

Laura Beste: This is Laura Beste. Can I just ask a question for clarification? Based on what Susan asked from the Committee when we are approving these agents, we are just approving them as an addition to the formulary, not their place in the formulary, is that correct?

Donna Sullivan: Correct.

Laura Beste: And then who decides their place within the formulary?

Donna Sullivan: So this is Donna. So after you make your motions, we have these, like I said, split up into their relative drug classes based on their mechanisms of action, and then we do a cost analysis. If you say that they are safe and efficacious and interchangeable, we will draw the line and pick several, or one or two or more of the least costly products, and we will do that drug class by drug class to determine if they are preferred or non-preferred. And this is Donna again. Susan, to correct myself, cyclosporine is one of four drugs, at least for Dupixent, that is required for trying to get to Dupixent. So methotrexate, cyclosporine, azathioprine, and mycophenolate would all be our they need to try one phototherapy or systemic corticosteroid, or one of the immunosuppressants.

Susan Flatebo: This is Susan again. Maybe the provider would be able to say they would not be a candidate for that medication.

Donna Sullivan: Yes.

Susan Flatebo: Based on the side effect profile. Okay.

Donna Sullivan: If one of those drugs was not appropriate for them to take from a clinical standpoint, then that would be taken into consideration, yes.

Kavita Chawla: Kavita Chawla here. I guess the one aspect that I am struggling with a little bit is understanding. So we are calling them all safe and efficacious in that the

harms, specifically the safety part, where the harms do not outweigh the benefits? But it seems to me from this incredible drug review that was done that some seem to have safer adverse effect profiles than others do. Kind of linking back to what Susan also said. The four, I think, drugs that you listed on it, that at least one of them need to be tried in order to go into one of the monoclonal antibodies, all of them having a major immunosuppressive impact. And so is it, for example, taking the simplest one, taking a systemic corticosteroid? Yes, it will probably improve their severe atopic dermatitis, but because it is not something that can be used long term, is that considered a tried and fail under our language to get approval for one of the newer agents?

Donna Sullivan: So, at this time, systemic steroids are not required. And let me go back for a minute. We are talking about the Washington PDL here. So typically, the Committee does not make recommendations as far as our policies are concerned. It is just based on the preferred, non-preferred status. When we review the Dupixent policy or the atopic dermatitis policy, I think that is a better time for this particular conversation.

Kavita Chawla: So, the discussion regarding preferred versus non-preferred is that a recommendation that is discussed right now or that is also discussed at the time of policy discussion?

Donna Sullivan: We make the preferred and non. We make the motion of their safety and efficacy and their interchangeabilities as the P&T Committee separate in a separate motion and separate from the Drug Utilization Review Board, which discusses the actual policies for Medicaid.

Leta Evaskus: This is Leta Evaskus. The Washington PDL is used by Uniform Medical Plan and Labor and Industry. So the Washington PDL only has about 30 drug classes, which are the highest cost drug classes. And UMP and Labor and Industry will each make their own decisions about if the drug is included if it is preferred or not. But these are the suggestions from the Committee.

Donna Sullivan: And this is Donna. And for Medicaid, we follow your motion guidance, but we won't end up with the same preferred drugs necessarily as UMP and L&I would for these particular classes. And that is because of the Medicaid program. Costs are much, much different than the Uniform Medical Plan because of the Federal Rebate Program.

Leta Evaskus: This is Leta. If you don't feel that one of these drugs, or some of these drugs, is not safe and efficacious, you don't have to list them. So we can start this off here, and then if you want to include all of the drugs or just a few of them I can list those as safe and efficacious.

Jordan Storhaug: So this is Jordan Storhaug. I just kind of try to direct us here and try to talk about the safety and efficacy of it. I think right now, I would think we would be planning on listing all of the drugs reviewed as safe and efficacious. So that is probably where we are starting, so if people feel differently, please go ahead and speak up, and then maybe more difficult is what we decide to do about the therapeutic interchange, as well.

Laura Beste: So I am a little curious. This is Laura Beste. So why was cyclosporin and mycophenolate and some of the older medications not included on the previous review in 2018 but it is being included now because these are not new medications?

Donna Sullivan: This is Donna. The report has changed, so the original report only included the newer products. And the newer report, I think, included additional drugs. I am just trying to navigate to the actual report to see what this is.

Leta Evaskus: This is Leta Evaskus. In the motion here, what is previously listed would be just the drugs that are reviewed in that report. So the ones that are bold here are new on this report.

Laura Beste: Just a small note, there needs to be an E on mycophenolate on the end.

Leta Evaskus: Thank you.

Donna Sullivan: Yeah, this is Donna again. So we just expanded this report because a lot of these drugs are indifferent. They have multiple indications. Some of them are rheumatoid arthritis. They have a variety. So when we switch from having kind of what we call the TIMS report, and we broke them out by indication. With atopic dermatitis, we decided we wanted to be able to look at the comparative efficacy of these more expensive biologic drugs compared to the older. The products that were traditionally used for treating atopic dermatitis. And so that is why the older drugs were included in this particular version of the report.

Luke Dearden: And this is Luke from HCA. I work a lot on the UMP Plan, and we don't require these older drugs as a step-through to the newer drugs for use in atopic dermatitis if that helps. And by older drugs, I mean the cyclosporine, mycophenolate, azathioprine.

Donna Sullivan: This is Donna again. As far as therapeutic interchange goes, in the past when we have had drugs across multiple drug classes or mechanisms of action within a single report, the Committee has made comments that they are therapeutically equivalent and interchangeable within their own drug subclass. So the calcineurin agents would be interchangeable, the methotrexate and azathioprine might be interchangeable, and some of the other -mabs if you feel that they are interchangeable. It would not be like interchanging cyclosporine instead of chrysoberyl. That would not be happening.

Kavita Chawla: Kavita Chawla here. I think I like that suggestion of including a language of therapeutic interchangeability within the drug class if the rest of the committee also agrees with that.

Jon MacKay: This is John MacKay. I would just like to comment that I think I would caution some of the therapeutic substitutions of the older agents like azathioprine or mycophenolate, just given the need for therapeutic monitoring.

Laura Beste: This is Laura Beste. Along those same lines, too, could you make it a little more generic since it hasn't been reviewed? And some medications cannot be interchanged. You could say the medications could be subject to therapeutic interchange in the Washington Preferred Drug Class as appropriate. And then it could be a little more generic and then up for review later on.

Donna Sullivan: This is Donna, again. And we can say that. A lot of these drugs, you know, the older ones are generic, and they don't require prior authorization, so they are likely preferred already. So there wouldn't be interchange happening. Some of the other drugs, I think, for Medicaid, at least, tacrolimus and pimecrolimus, I think there is a significant difference in cost, and I forget which one is cheaper, so one is preferred, and one is not. So yeah. I think that is okay, but there is therapeutic interchange that happens at the pharmacy by the pharmacist who is dispensing the drug, and so we wouldn't have a way of saying when it is appropriate or not appropriate. We just know that we get a prescription. We don't know what it has been prescribed for. It could be for psoriasis for all we know.

Susan Flatebo: So this is Susan again. So Donna, are you saying it is better to leave that language out and not have it be not even say anything about medications in this therapeutic subclass can be subject to therapeutic interchange? Because it is going to probably happen anyway.

Donna Sullivan: I guess what I am trying to say is that if you want the pharmacist at the time of dispensing to be able to dispense a preferred drug instead of a non-preferred drug without having to contact the doctor to get a new prescription because that is what therapeutic interchange means, then you need to say that they are interchangeable. If you don't feel that they are interchangeable and you don't feel that it is appropriate for the pharmacist who is dispensing the drug to make that determination, then you can just say they should not be subject to interchange. But, for example, the calcineurin inhibitors, before you had mentioned the Committee had determined that those were interchangeable and that the other two products that were reviewed were not. So if you feel comfortable with the calcineurin agents but not the others, then you could leave it as it was stated before and just call out the calcineurin agents.

Jordan Storhaug: This is Jordan Storhaug. That is probably what I would be leaning towards doing is just having the calcineurin inhibitors subjected to the therapeutic interchange. And part of the reason why that is it probably doesn't matter for some of the old ones. And I don't know if I am convinced that there is not a difference between our monoclonal antibody options. I think I would want to be contacted and let them know that we were going to need to use another one.

Laura Beste: This is Laura Beste. I think at this point without having had the time to review that information I would not want to make that decision.

Susan Flatebo: This is Susan Flatebo. I will go ahead and do the motion then if there is no more discussion. After considering the evidence of safety, efficacy, and special populations for the treatment of atopic dermatitis, I move that abrocitinib, azathioprine, crisaborole, cyclosporine, dupilumab, mycophenolate, omalizumab, pimecrolimus, ruxolitinib, tacrolimus, tralokinumab, and upadacitinib are safe and efficacious for the treatment of their approved indications. The calcineurin inhibitors can be subject to therapeutic interchange in the Washington PDL.

Virginia Buccola: This is Virginia Buccola, and I second.

Jordan Storhaug: Thank you. All in favor, please say, "Aye."

Multiple speakers: Aye. Aye. Aye. Aye.

Jordan Storhaug: If anyone dissent, please say, "Nay." Thank you. So then I will kind of reach out to Leta. Do you think we want to take a lunch at this time and follow up on the second generations after anti-psychotics? Or do you think we [cross-talk]?

Leta Evaskus: This is Leta Evaskus. I have checked with OHSU, and our presenters are okay if we take a half-hour lunch now and then reconvene. So it is about 12:25. So why don't we reconvene at 12:55?

Donna Sullivan: Okay. And Leta and Jordan, this is Donna. We are going to reschedule the second-generation antipsychotics, and then just go on to the ADHD drug class, since it was a carryover from the last meeting. So we will try to follow the agenda as published from here on out.

Jordan Storhaug: Be back to the old schedule.

Donna Sullivan: Yep.

Jordan Storhaug: Sounds like a plan.

Donna Sullivan: Right.

Leta Evaskus: Okay, thank you. And I will put up the sign that we will be reconvening at 12:55.

[break]

Leta Evaskus: Hi. This is Leta Evaskus. Shannon and our next presenters, if you want to go ahead and test your cameras and mics, go ahead. Can't hear you, Shannon.

Andrea Vintro: Testing. This is Andrea Vintro.

Leta Evaskus: Yes. I can hear you, Andrea.

Andrea Vintro: Okay, thanks.

Leta Evaskus: Shannon, you could also call in with your phone. And while we are waiting for that, I will pull up the presentation.

Jordan Storhaug: I think we are just still waiting for a speaker. It might be like a connector with that. I can answer one question from the chat for our stakeholders. We will allow you to be able to unmute yourself right before it is your turn to speak. So being unable to unmute yourself right now is okay. Leta, do you think we are ready to go? Or do we need to work with Shannon still?

Leta Evaskus: Andrea, I guess that is up to you. I don't know who starts the presentation.

Andrea Vintro: I am starting, although, I think it might be great to have sort of confirmation because Shannon is the primary author going to be going through the findings, discussion, etc.

Leta Evaskus: Okay. The other thing is, when Shannon calls in, I am just going to need to know her phone number to unmute it. But let's see. There is only one on there.

Andrea Vintro: I think she had had troubles with her mic working with teams, so I don't know if anyone has any suggestions on that route.

Leta Evaskus: Curtis, I have unmuted you. Okay, now Laura can't unmute herself. Um, let's see. Laura, I would double-check that you are not double-muted on your computer and then also on your phone. Okay, Laura. Thank you, Laura Crocker. Fixed that. Curtis, I see your hand raised. I have unmuted you. If you can unmute yourself. Okay, and for stakeholders, I will unmute you when your name is called to speak. So don't worry about not being able to unmute yourself right now. Oh, Curtis cannot. Okay, then.

Curtis: All right. Thanks, Leta. It looks like I can unmute now. So Shannon is still trying to work this out. I know Andrea is up first. I would recommend that let's just go ahead and get going with the presentation. Andrea, you can kick off your section by walking through the background and methods. And if at that time Shannon is still having audio issues, I will go ahead and do the presentation for her for the findings and conclusions, given my audio seems to be working okay. How does that sound, Leta?

Leta Evaskus: That sounds good. And I don't know if it changes anything if I move Shannon -- what I just did for you -- if that would help her microphone at all moving to a presenter instead of just unmuting her. But I don't see Shannon. Hang on just a second. The list is probably longer. Okay.

Shannon Robalino: Hi. This is Shannon. Can you hear me?

Leta Evaskus: Yes!

Jordan Storhaug: We can hear you, Shannon.

Shannon Robalino: Okay. Great. Okay, I will go back to being muted for the moment, then.

Leta Evaskus: Okay, great. Okay. Thank you, guys.

Jordan Storhaug: Yeah. So with that then Andrea will go and start the topic of ADHD and allow you to start your presentation. Thank you.

Andrea Vintro: Wonderful. So everyone can hear me at this point?

Jordan Storhaug: Yes, we can hear you.

Andrea Vintro: Great! We are here. So thank you, so much. Yes, my name is Andrea Vintro, and very happy to be here to present this report titled Pharmacological Therapies for ADHD, with my colleague and first author, Shannon Robalino. So we can go to the next slide. So this report will be presented in the format that is outlined on this slide. So I will walk you across from left to right. So I will start out with some background on the topic to find a PICOs and key questions and then walk you through our methods section before I turn it over to Shannon, who will present the findings and then finish up with some discussion and items for you to consider. Next slide. So for some background. Attention deficit hyperactivity disorder (ADHD) is considered a common neurodevelopmental disorder that affects nearly 10% of children and adolescents in the United States and also from about 1% to 4.5% of adults, and this is according to a 2016 report by the CDC. It has also been reported that over 60% of youth with ADHD are being treated with medication, and 80% of adults are treated specifically with stimulants for their ADHD symptoms. And to note that in adults, prescriptions for stimulants have been on the rise over the past decade, not only for ADHD but also for anxiety and depression, with the largest increase in the female population between the

ages of 25 to 55 years. In 2013, the diagnostic criteria for ADHD were updated with important changes, including an increase in age for the onset of symptoms. So before the update, symptoms had to start on or before the age of seven, and now that has been pushed back up to 12 years. And also the number of symptoms required for diagnosis of ADHD in adults has been reduced from six to five symptoms. And these changes are really reflecting the newer understanding of how symptoms are manifesting in adolescence through to adulthood. Other diagnostic criteria for ADHD include symptoms that are interfering with functioning must also be present in two or more settings, such as the school, the workplace, or other social environments. And symptoms must not be better explained by a different mental health disorder such as anxiety or depression. And just before we go to the next slide, I want to draw your attention to the green dog-eared page icon in the upper right-hand corner of this slide and several upcoming slides. The page numbers listed within that symbol correspond to the pages in the full report where you can find details of the information that we are summarizing for you here today. Okay, so we can go to slide three. The core symptom domains of ADHD are listed here on the top. And their definitions and inclusion criteria were not changed with the update of that diagnostic criteria. However, the nomenclature did change. So rather than three subtypes of ADHD, they are now called presentations. And again, this is reflecting that new understanding for that fluidity of symptoms that they are seeing between the domains across the lifespan. So individuals with predominantly inattentive presentation are challenged with a lack of focus, attention to detail, and disorganization when trying to complete tasks or follow instructions. For those with predominantly hyperactive-impulsive presentation, fidgeting, impulsivity, and the inability to sit or stand still for longer periods of time are the most common symptoms. And these behaviors also increase the likelihood of injury caused by accidents. And for those with a combined presentation, of course, symptoms of both inattention and hyperactivity, impulsivity are sort of equally present. Comorbidities with other psychiatric conditions are also common in persons with ADHD and that overlapping of symptoms. These conditions can present real challenges for clinicians to diagnose and treat appropriately. In children and adolescents, the most common comorbidities are oppositional defiant disorders, learning disorders, and also anxiety. And in adults, the most common include depression, anxiety, and substance use disorders. So treatments for ADHD can include stimulants and non-stimulant medications, of which there are 31 drugs currently approved by the FDA. Behavioral interventions including skills training and cognitive behavioral therapy (CBT) are also used to treat

ADHD and do note that clinical practice guidelines do specify that behavioral therapy should be the first line of treatment for preschool-aged children and also be included in the overall treatment for older children who are also on medication. Slide four, please. And so, like many other health conditions, the literature does identify disparities for the diagnosis and treatment of ADHD. And these disparities have been found across different race and ethnic groups, genders, age, socioeconomic levels, as well as geographic distributions, such as individuals between rural and urban environments. In general, historically, marginalized children, particularly those identified as Asian, Alaska Native, or Native American are less likely to be diagnosed with ADHD and less likely to receive pharmacotherapy. Other examples in studies are showing that children who are identified as black are more likely to receive behavioral therapy than other races and ethnic groups. However, they are less likely to ever be initiated on medication. Females are also less likely to be diagnosed with ADHD, and if they are, they are less likely to be prescribed stimulants. And evidence does suggest that different symptom presentations between gender types and gender bias among clinicians are potential reasons for these disparities across gender. Slide five. So there are some differences in the patterns of prevalence and treatment for individuals who are covered by Medicaid compared to the national cohort. A recent report by the Office of the Inspector General identified a higher prevalence of ADHD in children covered by Medicaid of approximately 13% in a 2014 and 2015 cohort, and this was compared to the national average of 5%. A large study of Medicaid-enrolled children, which was published in 2017, found that children identified as African American were less likely to receive adequate follow-up if they were prescribed medication and were more likely to discontinue and disengage from treatment compared to those identified as white. Another study found white male children living in a two-parent household were more likely to be assessed and treated for ADHD compared to their non-white female and single-parent household counterparts. And this was even more pronounced within the population of children enrolled in Medicaid. Gender and racial patterns of disparity seen in children also appear to be similar in the adult Medicaid population. And this last bullet point here refers to a study that found also large variations in treatment regimens in adults of Medicaid beneficiaries across different states. Next slide. So on this and the next few slides, I will go over the parameters and methods that we used to conduct this report. We start with population comparators and study design of the PICOS on this slide. So our population included any individuals with any of the three presentations of ADHD. For comparators, we were primarily interested in studies with head-to-head comparisons of different

drug treatments. However, for the more recently approved drugs that were not included in the last update of this report, we did include placebo-controlled trials and other standards of care such as behavioral therapy as comparators. So this will refer to any new drug that was approved after January 2015, which was that end search date for the last report update. We also did not include studies that compared a brand name with its generic equivalent or compared multiple doses of the same medication to each other, or explicitly included and focused on multimodal treatments like medication plus parent training, for example. And then for study design, we only included randomized controlled trials or RCTs. And just to note that in the previous report on this topic, they also included observational studies. So just wanting to confirm and remind you that those study types were not included in this current report. To slide seven. So on this and the next few slides we have a list of drugs that are included for our interventions of interest, I am not going to read every item here on this list. They are here for your reference, but I do want to just orient you to the slide. So at the top, starting on the left-hand column, we have the generic name or primary ingredient of the drug, followed by the brand name in the middle column, and then the date of FDA approval in the far-right column. The interventions in bold indicate new drugs approved since the last update of the report. And your eyes are not deceiving you. Yes, all of the drugs listed here are in bold. So this list is also an order of FDA approval with the most recently approved drugs listed at the top, and then also by drug category so shown in that yellow sub-header. In this slide, we have the drug category of stimulants, of which there are 27 different brands of stimulants. And I do want to mention here, what likely many of you know, that many of these drug brands contain the same active ingredients, but they have some chemical tweaking or additional compounds that allow for a novel delivery system that may allow for an extended or sustained release, for example. Next slide. So this slide, and then we can go to slide 10, that list continues. So on slide 10, here at the top, we have the category of non-stimulant drugs. Still looking at the interventions and you can see that viloxazine hydrochloride with the brand name Qelbree is in bold since it was recently approved by the FDA. That is right, yeah, in April of this year. And next, we have the drug category of Off-label treatments. And just to mention that the FDA approval date in that right-hand column, of course, is for the condition that it was originally indicated for these drugs, not for ADHD, of course. And so here on slide 11 is the last slide describing our PICOS for this report where we list the outcomes of interest. For efficacy and effectiveness, we included selected measures for symptom response, functional capacity, or performance as an academic or

work performance. We looked at quality of life. So this was for the patient as well as for the family, caregivers, and teachers. We looked at time to onset of effectiveness and also the duration of effectiveness. Then for harms, we included overall adverse events, discontinuation of the study due to adverse events, and then also serious adverse events. And then we also looked at misuse and diversion outcomes, including those listed here. Next slide. And here we have our four primary key questions for the report. So we asked about the evidence for effectiveness at harms of the FDA-approved and off-label pharmacological treatments for ADHD. We asked about the potential differences in effectiveness and harms across demographics, including across age, race, and gender groups, for example, and also across populations with different comorbidities. And finally, we look for any ongoing studies. So next, we will move to slide 13. So here we have a high-level overview of our methods. So from the previously commissioned reports, we identified all the head-to-head trials for drugs that are currently being used for the treatment of ADHD, and the head-to-head trials of any off-label drug interventions, and then move them forward for this report. And then all of the study characteristics and outcomes data from those studies that were presented in that prior report were cut and pasted basically into the respective sections for this report. And then if important information was missing, we did review those publications more thoroughly and added any information, as necessary. And then we searched Ovid MEDLINE, the Cochrane Library, and other internet sources for studies within the date limits of January 2015 through August 2021. And we also scanned reference lists of relevant systematic reviews for any additional studies. Then for ongoing studies, we searched clinicaltrials.gov and the Cochrane Database. And then for quality of evidence, we used two independent reviewers to conduct risk of bias assessments for studies that were identified from our database searches. And then for those studies that we moved forward from the previously commissioned reports, the risk of bias assessment was also moved forward. But we did adjust those assessments after reviewing for any conflicts of interest from study authors or funding of the study because this was not included in those earlier assessments. So, for example, if there were meaningful conflicts of interest of drug companies providing financial support to the authors or funding the study, which would have further increased the risk of bias of that study. We also conducted graded quality of evidence assessments on five select outcomes. And we did decide to limit the studies that were assessed for each grade outcome to those that included a minimum treatment period of eight weeks with or without follow-up. And this was done for a couple of reasons. First, it is well known that most

pharmacotherapies for ADHD do show immediate effects; however, they may not be maintained over time. And second, it is recommended that these drugs be titrated over a four- to six-week period until that optimal dose is achieved, and then that would leave a very short window to perform the actual study if the total length was less than eight weeks. Next slide. So as a reminder, DERP assesses the methodological quality of included studies that have been published in peer-reviewed journals using standardized assessments of risk of bias, which results in ratings of low, moderate, or high risk of bias, and you can see those definitions listed on this slide. In the bottom of the slide, the asterisk indicates that those adjustments for risk of bias were made on those studies that we moved forward from the prior reports. And then slide 15. As mentioned, we used that grade approach to assess the quality of the body of evidence for our outcomes of interest, and we selected those five at the top of the slide to be rated. So the body of evidence, which is that group of studies that look at a particular outcome. It is assessed based on the consistency of the findings across the study, the precision of the effects, any study limitations which are essentially captured as the risk of bias in the studies, and the directness, or generalizability of that evidence. These assessments are then summarized as a rating of high moderate, low, or very low quality of evidence, with bodies of RCT evidence starting at a high rating by default and then could be downgraded one or more levels for any concerns in those domains that I just mentioned. And these ratings correspond with a level of confidence that raters have and how closely an estimate represents the true effect of an intervention for an outcome. And each level is explained here on this slide. So thank you all for your attention. And I am going to stop here and let Shannon continue.

Shannon Robalino: Thanks, Andrea. Hopefully, you can all hear me okay. I was having some trouble with my mic. So I will move into the Findings section. If we can go to the next slide, please. So, this presentation as well as the report is an alphabet soup. There are a lot of abbreviations, and these ones are those that appear in this presentation. There is a full list of abbreviations in the report. But you should be familiar with most of these, as they refer to abbreviations for the drug names as well as some of the common tools used for diagnosis and response to treatment. If we can go to slide 18, please. So as Andrea said, we did a systematic review, and that meant we searched in bibliographic databases as well as pulling forward the head-to-head trials from previous reports. So you can see we started out with around 2000 results from the databases and pulled forward 78 studies from those previous reports. Once we filtered through everything during our screening for the title abstract and

full text, you can see at the very bottom there that we ended up with 70 studies across 96 publications; 26 of these studies are new to this review, and 44 were brought forward. Next slide. So this is just a quick overview of the findings of how the publications broke down. So I will just orient you to this table. You can see down the left-hand column are the comparators. So for example, stimulant versus stimulant or stimulant versus non-stimulant, followed by the number of trials for that category, the study size range, the total number of participants, and the range of study durations. So you can see for the stimulant versus stimulant category, there were 34 trials with a total of just under 4000 participants. And the first stimulant versus non-stimulant, however, there are fewer trials, 20 trials compared to the 34. But there were about 500, 600 more individuals in those trials. And just for this slide, I have combined the newer drug treatments. So those are the stimulant and non-stimulant treatments versus placebo, just for Brevity's sake here. We can go to the next slide. So again, the 70 studies, 26 of them are new since 2015. A majority of the studies did include US participants. The risk of bias for about a fifth of these studies was moderate, with the remainder having a high risk of bias. So 56 of the 70 studies had a high risk of bias. This is commonly due to industry funding, including extensive involvement in the trial by pharmaceutical company staff as well as methodological issues. For example, they may have had a short duration of only one or two weeks. Or if it was a crossover trial, they had no washout periods between crossovers. The majority of participants across all trials tended to be male children identified as white, who had the combined presentation of ADHD. Slide 21, please. So there are 13 new treatments since 2015, but only four of those treatments were reported in the new evidence; 12 of these are stimulants and one is a non-stimulant. For the newer treatments, there may be more that were studied, but most studies did not state the brand name of a drug, so it was difficult to determine if any of the newer drugs were also included in these newer publications. So Mydayis, which is an extended-release methamphetamine salt was compared to immediate-release methamphetamine salt in adults and adolescents in two small studies. And in the adolescent study, they found Mydayis worked better than the immediate release, but in adults, there was no difference between the two. And then the remaining three new drugs that were included here were Adhansia and Jornay, which are both stimulant medications, and Qelbree, which was that non-stimulant [indistinct] only compared to placebo. So the overall results, we did find that ADHD symptom reduction occurred regardless of the active treatment received and regardless of other personal characteristics such as age, gender, and any other comorbidities. The MCIDs for those who are not

well defined. There are some studies that have linked two diagnostic tools, the ADHD-RS and the CGI, the Clinical Global Impression Scale that was described in a 2010 study. So this is where some of these trials have got their MCIDs, but the trial investigators have then set the threshold for improvement from baseline. So this will usually range between 20% to 50% improvement from baseline to determine if it was an MCID in terms of the head-to-head trials. So this could be a stimulant versus another stimulant, or stimulant versus a non-stimulant. There was no treatment that proved to be better in general. There was one treatment, the non-stimulant atomoxetine when it was compared to several stimulants was found to be inferior Performance and quality of life outcomes were rarely reported. And as you are probably aware, adverse events are very common with these types of treatments. So, a majority of participants did experience at least one adverse event, but serious adverse events and discontinuation due to adverse events were rare. Move on to the next slide, please. So this is the certainty of evidence or the grade table here. It is just a summary here and let me orient you to this slide. So again, down the left column there you can see the comparators, stimulant versus stimulant, for example, as well as the total number of trials in that category. And then across the column, you can see symptom response, performance, etc. So these were the five outcomes that we assessed for certainty, and it also includes in each of those boxes the number of trials that met that qualification of having at least eight weeks of treatments with that particular outcome. So you can compare across the five outcomes in a particular category, so across stimulant versus stimulant, you can compare the symptom response, quality of life, discontinuations, etc. Or you can compare it down the column between comparator, so you can compare the stimulant versus stimulant symptom response to that of the stimulant versus non-stimulant symptom response. You will also note an absence of green dots, so no outcomes had a high certainty of evidence. And these will be repeated in the main part of the Findings sections. So we can go to the next slide, please. So these are the new FDA-approved treatments. You can see that the bulk of them are stimulant treatments. And the Qelbree that sat there all by its lonesome in the bottom of the second column is the only new non-stimulant since early 2015. So if we can move into the next slide, we can jump one more. So we are going to start with the placebo-controlled trials. And first up are the stimulant versus placebo trials. And we had identified six of these trials across nine publications. And you can see, again, across the top of this slide to see the study size range as well as the total number of participants and the study duration. So you will see that all of these studies had a one to four-week duration, therefore, none of them

qualified to be assessed with [indistinct]. All of these trials were conducted in the US. And there were two drugs here, the Adhansia and Jornay. So these are two of the 12 new stimulant drugs. There are four RCTs for Adhansia. Adhansia is a multi-layered released methylphenidate. One of these was in children only, and three were in adults. And while these adult studies often included individuals up to the age of 50 or 60, you can see that the mean age there for these adult trials was around 36 years old, so it is still leaning towards the younger end of the range. For Jornay PM, which is a delayed-released and extended-released methylphenidate. There were two trials. Both of these were also conducted in children only. And you can see that the mean age was eight years old. All six of these trials had a high risk of bias. So if we can move to the next slide, please. So let me just take another moment to orient you to the slide because we will be seeing this similar layout throughout the rest of the presentation here. So again, down the left column, we have the comparators. So we have in this case, the multi-layer released methylphenidate versus placebo, followed by the age range of that trial, the number of trials, the total number of participants, and then any symptom response, in this case, scales that were our tools that were used to determine symptom response. When items are in bold, so the MLR-MPH is in bold because that performed better than placebo. And then in the far-right column where the diagnostic tools are, you can see the bolded text there occurs when there have been statistically significant results. So as you can see, overall, active treatments were performed better than placebo across a number of different diagnostic tools to determine symptom response. Next slide, please. So in terms of any performance outcomes, there were four of the trials did report the performance outcomes, and they all use the same tool, PERMP. And again, those active treatments performed better than the placebo when they measured performance, so it was either workplace or classroom performance that was evaluated in a simulated environment over a single day. They may have conducted more than one session and averaged the results from these trials. If we could move to the next slide, please. In terms of quality of life, you can see that there were three trials here. The first row that the MLR-MPH was the adults. There were two of those trials, and in terms of quality of life, they measured sleep quality in these adults and found no difference. However, in the study in children of the delayed-release, extended-release. This is Jornay PM and children, they did find that caregiver strain was reduced in those children who received the active treatment. Next slide, please. So in terms of any adverse events, and those related outcomes of the serious adverse events, and discontinuation due to AEs, we will start with Adhansia, that multilayer-release methylphenidate. So adverse events

were more common in those participants who received the active treatment versus placebo. You can see the bullet points there demonstrate that about a quarter of the children who received the active treatment had at least one adverse event, as well as half of the adults. The studies did not always include details of what these adverse events were, but where they did, we have included those details. So, for example, you can see here in the adults, that headache, insomnia, dry mouth, decreased appetite, and nausea were the most common of the adverse events experienced. Serious adverse events were rare. There is only one in adults receiving Adhansia. Again, details were not provided by the study authors. Discontinuations due to adverse events were also rare, as you can see, there were eight in the adults. But again, no details were reported. Move on to the next slide. So this is the stimulant Jornay, which was compared to placebo in children. Again, you can see that a number of adverse events occurred, but they were also highly common in the placebo group, which is interesting. And those common adverse events included headaches, insomnia, and decreased appetite. Neither serious adverse events nor discontinuations due to adverse events were reported for these two trials. Next slide, please. So we will move on to one more slide onto slide 32. So now, these are the non-stimulant compared with placebo trials. So these are the new non-stimulant or [indistinct] non-stimulant Qelbree, viloxazine compared with placebo. There are five RCTs that we identified with a total of about 1600 participants. Treatment periods ranged from six to eight weeks. So a majority of these studies did qualify for grade assessment. Again, all of these studies were in the US, and all compared Qelbree to placebo. Three of those trials were in children where doses ranged from 100 mg to 400 mg per day. And I just want to note here that I am calling out specifically the [indistinct] and ethnic groups of the African Americans compared with white children because it has been generally pretty uncommon for trials to enroll large numbers of non-white participants. So this is where we are beginning to see a little bit more parody where they are enrolling larger numbers of non-white participants. So similarly, in the two trials for the adolescents, there were doses of Qelbree of 200 mg to 600 mg per day. And again, you can see that this trial also enrolled a large portion of African American adolescents. All five of these RCTs had a high risk of bias. Slide 33. So this is the certainty of evidence. There is a little bit more detail here than on the overview slide at the beginning of the Findings section. So you can see the five outcomes of interest here and the tabs, so to speak, are color-coded. So for symptom response, there was a low certainty of evidence that two of the RCTs out of five qualified for this review of this particular outcome assessment. And if you look at the rest of these you can see there

were no eligible studies for performance. And then for quality of life discontinuations due to AEs and serious AEs, these all had a very low certainty of evidence. There are more details, of course, in the report, giving information on why things were downgraded to where they are. Next slide, please. So again, we are going to start with this non-stimulant Qelbree versus placebo, and we are going to start with those trials that were in children. You can see that the comparators range from 100 mg to 400 mg and that all of those performed better than placebo. You can see on the far-right column, where we start looking at the symptom response, everything is not bold, here. So, for example, for viloxazine at 100 mg, you see the mixed for clinician-rated outcomes. This means that the clinicians use multiple instruments. So for example, they may have used the CGI and ADHD-RS instrument and found statistical significance in one instrument but not in the other, so that means the results were mixed. You can see there that for parent-rated symptom response, there was statistical significance, and you can see that throughout again that the active treatment tended to have improved response compared to placebo. Next slide, please. So similarly, in the adolescents where doses range from 200 mg to 600 mg, you can see for both the 200 mg and 400 mg doses the clinician-rated symptom response showed significance but not for the parent-rated symptom response. And then for the 600 mg dose, there was no difference when compared with placebo. Next slide, please. In terms of quality of life, all of these studies measured parental stress. And you can see that for the most part, none of these trials found any difference in parental stress when comparing the active treatments to placebo, with the exception of that 400 mg dose where you can see there was one trial in children that had some reduction in parental stress. Next slide, please. So for the adverse events and those related outcomes. Again, adverse events are common. So most participants experienced at least one adverse event. You can see that about half of the participants who received the active treatments had an adverse event, but you will also notice that for the placebo groups, they also reported high rates of adverse events. These common adverse events are loss of appetite, sleep disturbance, drowsiness, etc. For the serious adverse events, they were again, very rare, with only seven reported in children and two in adolescents, as were the discontinuations due to adverse events, with a total of 45 reported across these trials. Neither the serious adverse events nor the discontinuations due to adverse events were reported. The details were not reported. Move to the next slide, please. So we are going to get into the head-to-head RCTs now. So if you could move on to slide 39. So as a brief overview, we are going to start with the stimulant versus stimulant RCTs. So there were

34 across 45 publications, with just under 4000 participants and study durations of one to 16 weeks. Seven of these studies are new to this report. The remaining studies were brought forward from the previous report and spanned from 1975 to 2014; 14 of the trials are traditional RCTs, but the majority of them were crossover RCTs with very short treatment phases and generally no washout periods between. They did tend to wash out before the beginning of the trial, but when they did those crossovers, they immediately started the next treatment rather than having any washout between those treatments. So the majority of these RCTs were in children and adolescents, though you can see there that even when they enrolled adolescents, the mean age is still skewed towards the lower end of the range. There were four studies that enrolled adolescents only, and then there were three studies that enrolled adults. Again, you can see that the mean age used towards the lower end of the scale when they enrolled adults up to the age of 60. About three-quarters of these trials were conducted in US populations or included US populations. And most of these trials had a high risk of bias. Again, this tends to be due to industry involvement, as well as methodological issues such as those short treatment periods and lack of washout or blinding. The remaining four did have a moderate risk of bias, and this is due to industry involvement. Next slide, please. So of these 34 RCTs, there were only three that qualified for a graded assessment. So you can see those results here. Again, the red indicates a very low certainty of evidence, and the orange for the serious AEs on this slide are for a low certainty of evidence. Next slide, please. So from here on out we are going to focus on only the new studies. So I have highlighted those in a green box that you should be able to see on this slide. So we will start here with these new trials published in 2015. And you can see the number of trials here. There is a total of four. Again, you can see that there were very mixed results. So for example, the immediate-release mass versus an extended-release mass in adolescents, the extended-release mass did prove to reduce symptoms more than the immediate release. But the actual scales that were used there was some mix between the clinicians and the individuals when they self-rated their symptom response. You can also see that in the adult trial of immediate-release versus extended-release that there was no difference in symptom response. And for lisdexamfetamine versus another type of oral-release methylphenidate, there was lisdexamfetamine performed better, but there was, again, that mixed result of symptom response. And lastly, the last group of RCTs there are in children and adolescents comparing methylphenidate, a form of methylphenidate to either another form of methylphenidate or lisdexamfetamine and found no difference. Move to the next slide. So these are studies from the previous

reports, or they were published prior to 2015. They are here for completeness so that you can compare the findings of those new studies and these older studies. In this presentation, briefly, you will see that the older studies have similar outcomes compared with the newer studies, and the newer studies haven't moved the needle in terms of efficacy of these treatments. Next slide, please. So in terms of performance, on this slide, you can see there are four rows. Three of these are newer trials. So there are three small studies with under 100 participants each measured performance. You can see that in the children and adolescents, so that is the first and third line. They used an academic performance scale and found some statistical significance for the extended-release methamphetamine salts or the oral-release methylphenidate. But for the adults, there was no difference in workplace performance. And as a reminder, these were in simulated environments over either a single day or multiple days where they averaged the outcome. Next slide, please. So for quality of life, there is a single new study that measured the parental stress and did find that with the children who received the OROS-MPH, the parental stress was reduced compared to those who had children on the immediate-release methylphenidate. Medication adherence is infrequently recorded across all trials. So here we have two RCTs that compared the immediate-release methamphetamine salt to an extended-release and had higher adherence in both adults and children for the immediate-release versions of these methamphetamine salts. Next slide, please. For the adverse events, I won't bore you by repeating them, but they are common across these medications, as you are aware. In terms of serious adverse events, there were less. They were also rare, with less than 1% of participants experiencing a serious adverse event. So there are only 10 reported across nine RCTs with just over 1000 participants. Discontinuation due to adverse events were also rare with around 3% of participants who experience discontinuing the trial due to an adverse event. So the most common were decreased appetite, facial tics, and headache. Most of these did occur in children and adolescents who received the lisdexamfetamine or a long-acting methylphenidate. Next slide, please. And we can move one more forward. So these are going to be the stimulant versus non-stimulant head-to-head trials. So we had 20 RCTs across 30 publications. Again the study size ranges there and with about 4600 participants across these 20 studies. The duration of the studies is 2 to 26 weeks. Eight of these studies are new to this report, and the remainder were previously reported. The majority of these trials were traditional RCTs. There were only four that were crossover RCTs with short treatment phases of 2 to 6 weeks. So as we saw in the stimulant

versus stimulant group, even when the study is enrolled. We have jumped out of the slides it looks like. It should be on slide 47.

Leta Evaskus: This is Leta. Sorry about that.

Shannon Robalino: That's okay.

Leta Evaskus: My computer just froze. Just a minute.

Shannon Robalino: It is one of those days. The sun is coming out here, so that is something. We should be on slide 47.

Leta Evaskus: There we go. It wants to come back. Okay. Hang on.

Shannon Robalino: I will take this opportunity to have a sip of water.

Leta Evaskus: There you go. It is open. It just won't stay on my screen.

Shannon Robalino: Oh yeah, it looks like PowerPoint is having a meltdown. Everybody take a moment to stretch.

Leta Evaskus: Yes. Okay.

Shannon Robalino: One of my cats is wanting join in the fun.

Leta Evaskus: It won't let me move.

Shannon Robalino: Are you able to give me control at all?

Leta Evaskus: Oh, wait. It came back. Hang on just a second. Okay. We are on 44. Is that correct?

Shannon Robalino: 47.

Leta Evaskus: 47.

Shannon Robalino: Perfect. Okay, fingers crossed. We can get through this, you guys. Okay, so I will just kind of back up. So we had 20 head-to-head trials here for the stimulant versus non-stimulant category with about 4600 participants. Sixteen of these trials were traditional RCTs with four that were crossover

RCTs. In terms of age group, you can see that the majority of them enrolled children or children and adolescents. Even those that enrolled adolescents still had a low mean age of like seven years, and two enrolled adults. Again, the mean age was towards the lower end of the scale, though one of them did include a mean age of 41 years. Just over half of the trials included some US participants and, again, about half of the trials had a high risk of bias due to industry and methodological concerns. It had a moderate risk of bias. Next slide, please. So on slide 48, here, we can see the certainty of evidence. And there were 13 of the 20 who had at least eight weeks of treatment and qualified for at least one of the outcomes assessed here. So you can see that for symptom response, there was a moderate certainty of evidence. This is the highest level of certainty of evidence we had in this report. And then for the performance and discontinuations, these are both very low, and for serious adverse events, this was a low certainty of evidence. Slide 49, please. So again, we will focus on these newer studies. So those in the green box, generally there is no difference found. You can see in that first row this was the majority of those trials, eight of them with 1100 participants aged from 6 to 50, and this compared dexmethylphenidate to various non-stimulants including a combination of a non-stimulant given with a stimulant. In this trial, it was a four-arm trial with the second row here in ages 7 to 14. The participants who received the combination of a non-stimulant guanfacine and the dexmethylphenidate did have better symptom response compared to those who [indistinct] the non-stimulant on its own. And the bottom three rows are again the older trials here for your convenience. Next slide, please. So in terms of performance, you can see there was just one small trial that qualified for [indistinct] was a workplace performance in adults, and no difference was found in terms of those performance ratings. Next slide, please. In terms of quality of life, there was one trial of just 50 participants. These were all children, young adolescents ages 6 to 14. And they measured sleep in a subgroup of these children and found that sleep had improved in those who received the non-stimulant atomoxetine. In terms of medication adherence, this was reported only by two trials. You can see that in the first trial on that first bullet there the immediate-release methylphenidate compared to atomoxetine in drug-naive adults there was no difference in medication adherence. But in the second bullet point there, the stimulant had better medication adherence in drug-naive children than it did in those that received the non-stimulant. Next slide, please. So again, adverse events are very common, and the types of adverse events are as expected: loss of appetite, daytime drowsiness, headaches, etc. Children who received the combination of methylphenidate and clonidine, which is an antidepressant,

were more likely to experience an adverse event than if either drug was given on its own. And serious adverse events were again rare with less than 1% of participants experiencing an adverse event. And you can see that the majority of those serious adverse events occurred in those who received a stimulant. Slide 53. In terms of discontinuation due to adverse events, again, these were relatively rare. It looks like a large number there of 179 in 16 RCTs, but this is about 5% overall, and the majority of them occurred in the non-stimulant. It is kind of similar but slightly more in the non-stimulant atomoxetine. In terms of why participants discontinued due to adverse events, it really varied by the drugs. So here you can see the three drugs here: atomoxetine, lisdexamfetamine, and methylphenidate, and the different reasons why. The most common reasons that were given for discontinuation due to an adverse event, things like abdominal pain, chest pain, nausea, and rash for atomoxetine; agitation and tics for lisdexamfetamine; and decreased appetite, mania, etc., for methylphenidate. Move on to the next slide. And actually, it can go one more to slide 55. These are the stimulant versus off-label treatments. There were no new studies identified here. So we will go through this a little bit quicker. There were four RCTs that were brought forward from the previous reports that compared a stimulant to an off-label treatment of either bupropion or Modafinil. And you can see two of each. There were two studies under each of these two off-label treatments. And you can see that there were three of these studies that were high risk of bias, and one was a moderate risk of bias. Next slide, please. So again, these are the older studies, so I won't spend any time here. But you can see that the stimulant compared to an off-label treatment there was no difference. But these are all very small trials. Next slide. And again, adverse events were common, particularly in those who received the stimulants. And they differed by age group for the Bupropion. So drowsiness, fatigue, nausea, anorexia, dizziness experienced by children, whereas adults were more commonly experiencing dry mouth, headache, and insomnia. And discontinuations due to AEs were rare for Modafinil versus the stimulant. Again, the AEs were more common in the two stimulant medications compared with the off-label one, Modafinil in this case. And the reasons where the types of adverse events were different for the children and adults. Next slide, please. So this is the last section of the head-to-head studies, and then we will move into the ongoing studies. So if we can move forward one slide. So there was only one study identified. That was a non-stimulant compared to a non-stimulant. The original study was published in 2014, but there was a post hoc analysis published in 2016. So those are the results that I will discuss here. Again, please note that the age range of 6 to 17 years, but the mean age was 10.8, so

skewing towards that lower end of the scale. And in this trial, in particular, they had allowed a high proportion of individuals with a comorbid diagnosis, in this case, oppositional defiant disorder. And that was a rarity among these trials. The risk of bias for this study was moderate. Next slide, please. [Indistinct] with a certainty of evidence, we only had the one trial. And you can see that for symptom response, discontinuations due to AEs, and serious AEs, these are all considered to have a low certainty of evidence. Next slide, please. So this is that first line at the top that is outside of the green box. Those are the results from the trial that was originally published in 2014. So you can see guanfacine performed better than atomoxetine at that time. And this post hoc analysis stratified participants by whether they had had prior MPH use or if they were MPH naive and determine their symptom response. They did only compare that symptom response to placebo. So you can see that for those who had prior MPH use, there was no difference between atomoxetine and placebo, but there was for guanfacine compared to placebo with guanfacine performing better than placebo. And for those who were MPH naive, neither the act of treatments showed an improvement in symptoms compared to those who received placebo. Next slide, please. Again, adverse events super common in these treatments, the type of adverse events, unfortunately, are not reported in this trial. But you can see that large portions of individuals who received the active treatments did have at least one adverse event. The SAEs were rare as were the discontinuations due to AEs. Next slide, please. So we are going to look at the ongoing studies here. If we can go to slide 64. Thank you. So the first three lines here are head-to-head trials. They are above the solid green line. So the first row here is a stimulant compared with another stimulant, and you can see that is a larger trial in young adolescents and adults that should be completed soon, hopefully. And the next line is a stimulant versus a non-stimulant, methylphenidate versus atomoxetine, in children and adolescents. And the last one there, the head-to-head trial is atomoxetine versus guanfacine in children and adolescents. The last three rows on this slide are newer treatments compared with placebo. So the XR-MPH, in this case, is Adhansia, which was approved in 2019, and then the viloxazine versus placebo in the other two trials. I will just highlight that the very last row on this slide here, viloxazine versus placebo, is being conducted in preschool-aged children. Next slide, please. So we will move on to slide 66 and just wrap up here with the summary of the findings. So we found 70 RCTs. Of the 70 RCTs, 26 were published since January of 2015; 15 of these were head-to-head RCTs, and 11 were placebo-controlled trials of three of the newer drugs Adhansia, Jornay PM, both stimulants, and Qelbree, the non-stimulant. Most of the studies did

enroll male children diagnosed with the combined presentation of ADHD and who were identified as white. Overall, all participants who received an active treatment had reduced symptom response compared to the baseline. As expected, adverse events are very common in these drugs. But the serious adverse events and discontinuations due to AEs were, thankfully, rare. Few studies reported on performance, quality of life, or medication adherence. And I just want to remind you that in terms of academic performance and even some of the symptom response outcomes, there were discrepancies between either a clinician or teacher rating of the effectiveness compared to the parent or self-rated effectiveness and for their symptom response or performance. Next slide, please. So there are a number of limitations to this body of evidence. So the AAP recommends at least six weeks of treatment because of the titration needed to identify an optimal dose and to determine how effective that treatment is. So many of these studies had much shorter treatment periods, may have titrated the doses rapidly, or did titrate across a number of weeks but then only provided one to two weeks of optimal treatment. Studies often exclude comorbidities despite them being very common in this population, as Andrea addressed at the start of this talk. So there are common comorbidities like depression or anxiety, and these individuals with these comorbidities were only allowed to be part of the trial if they had mild symptoms and were not being treated for those symptoms. Performance was often measured during a single day. These were the simulated classroom and workplace environments, so they were followed by short treatment periods, but they proceed [indistinct] followed after a short treatment period of usually no more than 4 to 10 days and no washout periods [indistinct] will often be crossover trials. Next slide, please. So what about all these new drugs? As you recall, we have 13 newly approved FDA drugs for ADHD, and these have all been approved since January of 2015. So most of the studies did not report a brand-name drug. In terms of those that did, we are aware of four of the newer drugs that were approved did appear in these trials, and they were generally compared with placebo. So there were the 12 new stimulants. We had the Mydayis, the extended-release methamphetamine salts, compared to an immediate-release in two crossover trials, where the crossover trial with adolescents found that the extended-release, so Mydayis, performed better than the immediate-release. But this was not the case in adults, where there was no difference found. The other two new drug stimulants that were included here were Adhansia and Jornay PM, which were both compared to placebo and found that the active drugs were better than placebo and similarly with the single new non-stimulant drug, Qelbree, compared with placebo. Next slide, please. So I just want to

revisit the disparities that Andrea discussed in the introduction here. So despite the knowledge that there is a disparity in diagnosis and treatment, most studies continue to enroll a majority of male children identified as white. While the diagnosis and treatment gap is closing for females at any age, studies still are not enrolling this population, particularly the older females, and older females tend to be diagnosed in adulthood. I believe Andrea mentioned that it is common to be diagnosed from age 25 upwards if you are female. Studies also rarely conducted were rarely conducted in adults despite this increasing diagnosis, but there are two ongoing trials looking at the adult populations. And as Andrea mentioned in the introduction, adult diagnoses are outpacing those in children and adolescents now. Psychosocial treatment is recommended alongside medication, particularly in children and adolescents. And evidence suggests that the medication assists with the symptoms but generally not with quality of life or performance outcomes. The psychosocial interventions tend to help an individual learn skills to manage their condition, such as study skills, time management, or organizational skills. There is growing evidence that suggests that the biases that we are seeing between clinician and teacher evaluations of symptom response or performance compared to those of the parents or the individuals themselves do lie across racial, cultural, and gender lines. Next slide, please. So just to wrap up here with a couple of things to consider. There are some limitations with the instruments that are being used to determine whether treatments are effective. So for example, ADHD and most of these other scales have been developed and validated in white male children. There are also behavioral expectations that are maybe applied to gender, race, or cultures that may differ. So these instruments may not be useful in determining that. So for example, there may be a behavior that is considered okay in boys such as being outspoken and opinionated in the classroom, but this is not the case for girls. So that is a gender bias. And there are also similar biases along racial and ethnic lines. It is common for individuals to try multiple medications at different doses to find one that balances the treatment response and the adverse events. So there is a lot of [indistinct] here, as you are probably aware. And there are also changes over an individual's lifetime, so they may need different treatments or different levels of treatment depending on where they are during a particular point in their life. If they are changing from adolescence to adulthood, if they are experiencing different kinds of stress or social supports are reduced or not, they may require different levels of treatment. And then slide 71 is the last slide here. So prior authorization policies are really common with these treatments, particularly those that are stimulant treatments. So things to

consider -- are those prior authorization policies aligned with current guidelines? So for example, offering both medication and psychosocial supports and allowing for that [indistinct], can a patient change their medications? So if it becomes no longer effective or they develop a serious side effect, how easy is it for a patient to change the medications? Or if they are experiencing life circumstances that require them to have a different medication or a different level of medication? And lastly, what about how it allows an individual to engage and continue their treatment? If they have to get prior authorization to change the dose, does this mean that they may have a break in treatment and then maybe fall out of treatment completely? And this is especially concerning for those who [indistinct] or who identify as non-white, where it is common to see a disconnect between engagement and continuity. And that is that for me. So I will turn it back over to you for any questions or follow-up.

Jordan Storhaug: See if we have some questions, then go ahead and let us know. But we will go ahead and get ready for our stakeholder input, as well. And so first up is Lance Lewis of Corium.

Lance Lewis: Okay. Hi, everybody. Can you see me, hear me okay?

Jordan Storhaug: We can hear you. [cross-talk]

Lance Lewis: [Cross-talk] Okay, sounds good. Well, thank you, everybody. My name is Lance Lewis, and I am the Field Medical Affairs Director with Corium, and today I will be presenting on the new ADHD treatment, Azstarys, and I would like to focus my presentation today on three key areas. First, the unique characteristics of the Azstarys; second, the duration of action and efficacy of Azstarys; and third, the important safety information. So let's start with the unique characteristics of the Azstarys. So Azstarys is a CNS stimulant approved in March 2021 for the treatment of ADHD in patients six years of age and older, including adults. Azstarys is available in three dosage strengths equivalent to 20mg, 30 mg, and 40 mg total dexmethylphenidate. Azstarys comes in a capsule form and is administered orally once daily in the morning with or without food and can be taken whole or consumed by sprinkling contents into 15 mL of water or 2 tablespoons of applesauce. And this is important for patients who have difficulty swallowing capsules. Each Azstarys capsule contains two active ingredients in the following ratio: 30% dexmethylphenidate plus 70% serdexmethylphenidate, which is the first and only methylphenidate prodrug and only the second prodrug in the ADHD

space. Serdexmethylphenidate is a new molecular entity and classified as a Schedule IV controlled substance. However, Azstarys, itself, is classified as a Schedule II controlled substance as it contains 30% dexmethylphenidate, which is a Schedule II. Serdexmethylphenidate produces lower drug-liking effects compared to other Schedule II and Schedule IV controlled substances in human abuse studies. In fact, it was these studies that led to the Schedule IV designation for serdexmethylphenidate. So next, I would like to share some information regarding the duration of action and efficacy of Azstarys. With many ADHD treatments, there remain vulnerable periods of time with inadequate drug coverage either in the morning or early evening hours of the day. And so Azstarys' unique coformulation is designed to provide both early-onset within 30 minutes and extended duration up to 13 hours. Azstarys demonstrated a significant improvement in attention and behavior of children ages six to 12 years old, as measured by SKAMP-C scores in a laboratory classroom setting over a 13-hour period during the Phase 3 trial. So finally, I would like to share important information regarding safety. So Azstarys has demonstrated a safety profile consistent with that observed for other methylphenidate products, and Azstarys had no notable safety signals identified. The most common adverse events during the double-blind treatment phase of the Phase 3 study were upper respiratory tract infection, headache, and abdominal pain. No adverse events were considered serious. In a long-term 12-month open-label safety study, Azstarys did not have a clinically significant impact on height and weight, nor did it negatively impact sleep. Of course, these are always concerns associated with stimulants. For full prescribing and safety information, please refer to the Azstarys package insert, which can be found at Azstarys.com. I would like to thank the Committee for their time, and I would be happy to answer any questions you may have. Thank you, again.

Jordan Storhaug: Thank you. Next up we have Patrick Harvey from Supernus Pharmaceuticals.

Patrick Harvey: Here we go. Thank you. Good [cross-talk].

Jordan Storhaug: All right.

Patrick Harvey: Okay, thank you. Good afternoon. My name is Patrick Harvey with Supernus Pharmaceutical Medical Affairs. Thank you for the opportunity to make a few comments regarding Qelbree. I would refer you to our complete prescribing information for full product details, including our Blackbox warning in regard to suicidal thoughts and behaviors. As Andrea noted, there are over

31 drugs approved for the treatment of ADHD, but all but three of them are formulations of just two stimulant molecules, either methylphenidate or amphetamine. The diagnosis of ADHD in children is complex, and patients require more than just new stimulant delivery systems. Moreover, of the three FDA nonscheduled options, two of these have similar mechanisms of action, and physicians have indicated that there is a real need for additional nonscheduled options. Whether for consideration of stimulant abuse and diversion, or patient intolerance to stimulants or non-stimulants, or inability to swallow pills, Qelbree offers an important option for the treatment of ADHD. Qelbree is a new chemical entity and the first new molecular entity approved for ADHD in over 18 years. It is a nonscheduled, once-a-day medication that can be taken any time of the day. And it was approved by the FDA in April of last year. The mechanism of action of viloxazine and the treatment of ADHD is unclear; however, it is thought to be through inhibiting the reuptake of norepinephrine. We have additional data from animal studies and models and in vitro that suggest that the viloxazine increases dopamine, norepinephrine, but also serotonin in the prefrontal cortex. This increase in serotonin is not through reuptake inhibition but through direct action on receptors. This combined pharmacology makes viloxazine distinct from any FDA medicine used to treat ADHD. Additional clinical data that indirectly highlights areas unique to Qelbree that differentiates from another NRI, like Strattera, is we have no evidence of hepatic injury as evidenced by minimal AST and ALT elevations and liver enzymes across all trials. Qelbree has multiple metabolic groups of elimination and is unlikely to have any interaction with other drugs metabolized by CYP2D6, and phenotypic CYP2D6 metabolizer status appeared to have only minimal impact on Qelbree metabolism with only a 1.5-fold increase from the poor metabolizers versus the extensive metabolizers. Qelbree is contraindicated with MAOIs and sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range including theophylline. Qelbree has minimal impact on cardiovascular system with a supratherapeutic dose, and seeing no clinically significant [audio cuts out] cardiac [audio cuts out] suggesting it is not associated with a risk for cardiac arrhythmias. Medication adherence can also be negatively impacted due to pill swallowing difficulties, and Qelbree is the only non-stimulant that is designed to be swallowed whole, or the capsule can be opened and sprinkled with a small amount. So we ask that it be added to the [audio cuts out] Preferred Drug List. And I would be happy to answer [audio cuts out] any questions you might have.

Jordan Storhaug: Thank you. So we are open for questions. Leta, did you see anybody else who wanted to present as a stakeholder?

Leta Evaskus: This is Leta Evaskus. I don't see any other hands raised.

Jordan Storhaug: Okay. With that then we should be able to look at our motion.

Laura Beste: Hi. This is Laura Beste. I just had a question for Pat Harvey regarding the viloxazine. Did you know, did they look at studying it in conjunction with the stimulants?

Patrick Harvey: Yes, we just are finishing up the study with adjunctive therapy with stimulants.

Laura Beste: Okay.

Patrick Harvey: Yeah, it was a small study but, yes, we are doing it.

Laura Beste: Okay.

Jordan Storhaug: Leta, I wonder if you might be able to adjust it so we can see a little bit more of the motion.

Leta Evaskus: Can you still read it at that size? Let's see if I can go in between here.

Jordan Storhaug: It takes a little bit for it to update on my screen, so I can't tell you changed it yet.

Leta Evaskus: Oh.

Virginia Buccola: This is Ginni. I am just curious. I think the very top block is what I can't see, or we only [cross-talk] --

Leta Evaskus: [Cross-talk] maybe just to scroll down to the [cross-talk] --

Virginia Buccola: Oh, sorry.

Leta Evaskus: -- this motion.

Virginia Buccola: Okay.

Leta Evaskus: But yeah, there are two new drugs here.

Virginia Buccola: Okay. Thank you. I can see it now.

Jordan Storhaug: Perfect. Yeah, that is much better for me. Thank you.

Virginia Buccola: This is Ginni, I might suggest that we start crafting the motion by copying the statement used last time regarding amphetamines, both the short and long-acting we covered. So, yes, Leta, all the way down to -- yeah.

Leta Evaskus: Just the top paragraph first?

Virginia Buccola: Start there.

Leta Evaskus: Okay.

Virginia Buccola: Yeah. This is Ginni again. I'm curious, and I would like to hear from the other Committee Members. I can't see the words, but for the next section regarding non-stimulants -- there it is -- I don't know that there is anything convincing at this point in time to say that there would be a reason to move to viloxazine. Is viloxazine a prior to trying atomoxetine? So I don't know. Maybe, Leta, if you could cut and paste that second paragraph and put it up at the top so we could see it, and then the expert wordsmiths could help me. It would seem to me that in clinical practice, I don't know that I would go to viloxazine at this point in time prior to trying and failing atomoxetine. So if we might want to consider that as, or maybe we don't need to specify if it is on prior. Maybe Donna. Or is there somebody from HCA that can answer that question? Do we need to list as we have the non-stimulant atomoxetine listed by name as safe and efficacious and should be included as a preferred drug? But we have four non-stimulants? I can't remember if there is a reason why we have atomoxetine listed directly.

Donna Sullivan: I have a feeling we haven't reviewed this class in a long time.

Virginia Buccola: For a while? 2019.

Donna Sullivan: Yeah.

Virginia Buccola: Okay.

Multiple speakers: [Cross-talk].

Laura Beste: So this is Laura Beste. I do have some experience with this class of medications pretty extensively. And if you have a patient that would need a non-stimulant because of drug issues or drug use issues, you would want some of these non-stimulants as an option, especially in the teenage population with high schoolers or patients that are at risk for drug abuse. There would also be with viloxazine you might have somebody that had depression as a coexisting disease state where there might be some benefit. I don't know if there are studies on that, per se, because I haven't looked into that one as much. But that might also be a reason why you might choose that over another agent if you are considering that. I haven't looked specifically at that, so I don't know. So there might be a reason to keep that as an option for those patients.

Virginia Buccola: I would agree that it should be an option. I think at this point, the data that I have read is that atomoxetine and viloxazine are looking quite similar in terms of efficacy. So I don't think we would lose any access to an effective agent for people who need both anti-depressant and anti-anxiety effects and attention benefits. I just wanted to be sure that we would not miss an effective generic agent such as that atomoxetine. I would not want to bypass that and go directly to viloxazine at this point in time. That is really what I want to be sure that we reflect.

Amy Irwin: [Cross-talk] this is Amy from the Health Care Authority.

Laura Beste: [Cross-talk] So you are saying removing the -- oh, sorry, go ahead.

Amy Irwin: You had called out atomoxetine previously so that there was a non-stimulant that had to be a preferred drug so that there was an option to have something that was not a stimulant. If you want that not to be atomoxetine, or if you would want to have some flexibility there, you could say just make something along the lines of making it a non-stimulant. There must be one preferred non-stimulant, or you can call it out specifically. But that is why atomoxetine is called out there.

Virginia Buccola: Thank you for reminding me of that. I remember that now.

Amy Irwin: You are welcome.

Jordan Storhaug: This is Jordan Storhaug. I think clonidine and guanfacine, I think we would be disappointed if those were the only non-stimulants available. And so I think that there is probably -- I mean, I am assuming this with the cost -- but we probably would be satisfied with atomoxetine and the viloxazine being on the list. As long as one of those two, I think we probably would all be satisfied. I am with guessing cost it would be atomoxetine would be the one that would make the list.

Virginia Buccola: I would support that, Jordan.

Donna Sullivan: This is Donna. So what you could say is that there should be one non-stimulant that is not an alpha agonist preferred on the list.

Virginia Buccola: Yes. I like that.

Donna Sullivan: And maybe you can say at least one, and that way it doesn't make it look we can only have one.

Virginia Buccola: There you go.

Donna Sullivan: Thanks.

Laura Beste: Do we need to retain the language that it is not an alpha-agonist that is safe and efficacious?

Virginia Buccola: This is Ginni. I think that would be wise.

Donna Sullivan: This is Donna. And you want to then add for treatment of ADHD because it is safe and efficacious for what?

Virginia Buccola: Yes, for treatment for ADHD with a question that would not limit the use of the alpha-agonists for off-label treatment for anxiety or PTSD. Would it? [cross-talk] I mean, I know we are not talking about the treatment of those conditions right now.

Donna Sullivan: We don't have them on. I don't think anybody has those on prior authorization because they are generic, and the extended-release ones maybe, but I doubt it because I think they are all generic, as well.

Virginia Buccola: Then I would say leave it at ADHD. I just wanted to be sure we were not doing any unseen limiting of using those others for other categories.

Donna Sullivan: Mm-hmm. We are not. No.

Laura Beste: This is Laura Beste. Also, can we move the bupropion down to the non-stimulant section?

Virginia Buccola: I am wondering, is that grayed out because it is off-label?

Laura Beste: Probably, but it should be under non-stimulants, not stimulants. Correct?

Donna Sullivan: Yeah. It is an antidepressant. Yeah.

Leta Evaskus: I am going to look at the last paragraph.

Laura Beste: Or should it just be where it is listed like other medications rather than just other stimulants, other medications, or off-label medications?

Virginia Buccola: I was just going to suggest that, Laura. I would agree. Just change the title. Yeah. Just change the title of that cat [cross-talk].

Laura Beste: Complete.

Leta Evaskus: What did you settle on?

Virginia Buccola: Off-label treatments.

Jordan Storhaug: And it looks we probably just need to include that last paragraph, as well.

Virginia Buccola: This is Ginni. I don't want to put Laura on the spot, but if you want to make your first motion, I want to welcome you into the fray, if there is nobody else that has any other comments. Otherwise, if you are not ready, it is okay.

Laura Beste: I can do this. Okay. I need to see the top there. So I just read the whole -- okay. So this is Laura Beste, and after considering the evidence of safety, efficacy, and special populations for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), I move that methylphenidate-based and amphetamine-based agents of both long- and short-acting formulations are safe and efficacious. A long and short-acting formulation of each stimulant

should be the preferred drugs on the Washington State Preferred Drug List. No single stimulant medication is associated with fewer adverse events in special populations. The stimulants listed above shall not be subject to therapeutic interchange on the Washington Preferred Drug List. After considering the evidence of safety, efficacy, and special populations for the treatment of Attention Deficit Hyperactivity Disorder, I move that at least one non-stimulant that is not an alpha-agonist that is safe and efficacious for ADHD should be included as a preferred drug on Washington State Preferred Drug List. After considering the evidence of efficacy and special populations for the treatment of Attention Deficit Hyperactivity Disorder, I move that the alpha-agonists clonidine and guanfacine are safe and efficacious and that both of these agents should be included as a preferred drug on the Washington State Preferred Drug List. I so motion to accept.

Jordan Storhaug: Perfect. Thank you, Laura. Do we have a second?

Jon MacKay: This is Jon MacKay. I will second that.

Jordan Storhaug: Good. We are getting our new ones all participating. All in favor, please say, "Aye."

Multiple speakers: Aye. Aye. Aye. Aye.

Jordan Storhaug: Any opposed? All right, thank you. So with that, then I guess the work of the Pharmacy and Therapeutics Committee is all done, and we will adjourn and then reconvene as the Drug Utilization Review Board, and then the first item on the agenda for that is dealing with some antibiotics and a presentation from Umang.

Leta Evaskus: Okay. And Marissa, are you going to present now?

Marissa Tabile: Hi. This is Marissa. Yes, I will go ahead and present.

Umang Patel: Alright, perfect. Jordan, can I ask you just to confirm whether or not you can hear me?

Jordan Storhaug: You are a little quiet to me, but I can hear you.

Leta Evaskus: Yeah, same to me. You sound pretty quiet.

Umang Patel: Is that better by any chance?

Jordan Storhaug: Still a little quiet.

Leta Evaskus: It is the same.

Umang Patel: Okay. I apologize. I guess I am having some issues here. I will do my best to speak up. Is that better by any chance for everyone?

Jordan Storhaug: It is a little bit.

Umang Patel: I know there is a break coming up. During there I will go ahead and try to make sure that this gets fixed.

Jordan Storhaug: Sounds good. All right. Thank you.

Umang Patel: Okay. Alrighty. So then, we will be reviewing. The first subclass will be antibiotics. As just a reminder for the committee and some of the new members, what we tend to do is look at new clinical updates within the last 13 months or so. If there are any relevant, significant clinical updates, I usually present those. If there are no updates and guidelines, things like that, I usually try to keep them in the appendices, or they are available in the TCRs for the Committee's access there as well. And so on the next slide, we will be going over antibiotics and respiratory agents. Now, some of the new members may wonder why some of these are broken down the way they are. Magellan has specific therapeutic classes in subgroups that may be different from Apple Health. And so I do my best to show what our title is for some of these classes, and if they are broken out, what the Apple Health classes are. So for antibiotics, we will be going over inhaled aminoglycosides, inhaled monobactams, along with cystic fibrosis agents and CFTR potentiators.

Marissa Tabile: Umang, this is Marissa. Sorry to interrupt. I just wanted to make a note to the DUR Board that there was an oversight on my end. So the slides that you saw online or that you received did not have the CFTR potentiometers drug class listed. We did have a recent change to the cystic fibrosis class where we split out some of the cystic fibrosis agents versus having the CFTR potentiator separate. So just wanted to note that change and I have made that change also to the motions, as well, so that it is taken into account. I just wanted to let you guys know. Sorry, Umang, to interrupt. You can go ahead and proceed.

Umang Patel: No. No problem at all. Thank you. Okay, so we will go on to the next slide. Just a little bit of background we normally do. So cystic fibrosis is a serious autosomal recessive multiorgan disorder. It affects about 32,000 children and adults in the United States, and it is the most common fatal genetic disease in Caucasians. The median survival in patients is about 49 years with 80% of patients reaching adulthood. Children are anticipated to live up to approximately 40 years of age with current treatments. And in 2019, adults comprised approximately 56% of the cystic fibrosis population, while in 1989 they comprised approximately 31%. Mutations lead to the disease of the exocrine gland function, and so it results in the formation of thick mucus that builds up in the lungs, the digestive tract, and other parts of the body. The cystic fibrosis transmembrane conductance regulator (CFTR) functions as a chloride channel, and the mutations result in abnormalities of the chloride transport across the epithelial cells on the mucosal surfaces. Goals of treatment include maintaining lung function by controlling infection and clearing mucus, maintaining appropriate growth by providing nutritional support, and managing disease complications. On the next slide here, as I mentioned, the goals are threefold controlling infection, clearing mucus in the airway, and providing nutritional support. And then the CFTR modulators are the newest class of medications available for the disease and improve the chloride ion transport abnormalities. As I mentioned earlier, the guidelines are, as you can see, about seven to eight years old. And so they are here for the Committee's review and, again, in the TCR. But we won't be going over them, just here for completeness' sake. On the next slide, we will go over drug-specific updates. And, again, for some of the newer members, when you see bolded information here, the bold indicates the new clinical update. If there was a new indication and expanded formulation, a new Blackbox warning, or so on, so forth, I tend to just highlight and draw focus to the update, and we won't be going over all the clinical information as not all of it was updated. So on December 2020, the FDA approved Kalydeco for the treatment of cystic fibrosis in patients four to less than six months of age and weighing 5 kg or more, who have one or more mutations in the CFTR gene that is responsive to either ivacaftor based on clinical and/or invitro assay data. Previously, this was only in patients greater than six months or older. Again, no update to the indication aside from expanding the age. The dosage, obviously, has been updated to include pediatric patients four months to less than six months of age and less than 5 kg, and the dosing, as you can see, is 125 mg packet mixed with 1 teaspoon of soft food or liquid administered every 12 hours with fat-containing foods No changes in availability here, as well. And just some information for the Committee in terms of special

populations that is a pregnancy Category B as in beta. There is hepatic dose adjustment, there is no renal dose adjustment recommended for mild to moderate renal impairment, and there are no studies for moderate to severe renal impairment here. On the next slide here, we have Trikafta. A few updates in 2020 and 2021 for this medication. In December 2020, the PI update did expand the indication to include patients with cystic fibrosis who have a mutation in the CFTR gene that is responsive based on in-vitro data updated indication for treatment of cystic fibrosis in patients aged 12 years of age or older who have one or more F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in-vitro data. In June 2021, FDA approved this medication for patients six years of age through 11 years of age, again with the same F508del mutation. And in June 2021, they also approved a new dosage of the subgroup, so we have 50 mg of elexacaftor, 25 mg of tezacaftor, and 37.5 mg of ivacaftor co-packaged with ivacaftor 75 mg to accommodate the new dosing in the new age group. As you can imagine, the dosage is very weight and age-specific. So it is stratified, again, by age and weight. That can be found in the TCR in the PI. The availability hasn't really changed, we just now have an additional lower dose co-packaged formulation available as well. And on the last slide here, we have Symdeko, and in December 2020, PI updated to expand the indication for patient populations to include additional mutations in the CFTR gene that have been identified as responsive based upon in-vitro data. So I will go ahead and pause there for the Committee.

Marissa Tabile: Hi, this is Marissa, I am just going to go ahead and bring up the publication as well. So to our new DUR Board Members, the AHPDL is pretty big. It is over 500 classes. So for your reference for these meetings we just give you a snapshot of the classes that we are reviewing that are relevant to the meeting. So these are just the ones that we are reviewing today. So the particular classes of interest that I would want to point out are starting out on line four and line 11, which are antibiotics. And you can see which products we have preferred, which would be marked with a P, and N is non-preferred on our PDL. So I will go ahead and pause for about 30 seconds for you to see which products we have. You should also have received a copy of this, as well. And then like I mentioned earlier before, I did not include the CFTR potentiators as an oversight, which I apologize again. So we have updated this. This is the updated PDL. But you can see here that we have the Respiratory Agents: Cystic Fibrosis Agents, which starts on line 175 And then our CFTR potentiators start on 178. And you can also see which products we have preferred and non-preferred in both of those classes. And I can move to

the motion, Jordan, whenever you are ready, or if you have any questions about the AHPDL.

Jordan Storhaug: We do have a couple of stakeholders for this, too. So maybe that is where we should go next, I think. So first is Lisa Cambridge of Perry Respiratory. I don't know if we have Lisa there or not.

Leta Evaskus: This is Leta. I am wondering is Lisa Allen the correct Lisa? I am going to unmute Lisa Allen. Please let us know if you are Lisa Cambridge. Oh, if you could unmute yourself.

Lisa Allen: Hi. I am not Lisa Cambridge. I am Lisa Allen with Vertex Pharmaceuticals.

Leta Evaskus: I don't see Lisa Cambridge on here.

Jordan Storhaug: Alright, we will keep on looking. Let's go next to Kristin Dandurand.

Leta Evaskus: Okay. And Lisa, are you wanting to speak on this topic? Lisa Allen? Sorry, you are muted again.

Lisa Allen: Yes, please, at the appropriate time. Thank you.

Leta Evaskus: Okay. Why don't we have Lisa Allen go since she is on?

Jordan Storhaug: Got it. Lisa Allen, please, you have three minutes.

Lisa Allen: Thank you, very much. Good afternoon. Again, my name is Lisa Allen with Medical Affairs at Vertex Pharmaceuticals. Thank you for the opportunity to provide public testimony on behalf of the Vertex cystic fibrosis transmembrane conductance regulator modulators. CFTR modulators are the only cystic fibrosis medicines that work by targeting the underlying cause of CF, which is a defect in the CFTR protein. And as Dr. Patel nicely reviewed, there are four CFTR modulators approved for the treatment of CF based on age and genotype, including Trikafta, Symdeko, Orkambi, and Kalydeco. I am not going to [indistinct] updates that have occurred since he covered those so thoroughly, but I want to add that on October 4 of last year, section 6.2, the post-marketing experience was added to the Trikafta USPI, and section 5.1 Warnings and Precautions was updated as follows: Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving Trikafta. Avoid the use of Trikafta in patients

with preexisting advanced liver disease unless the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment. Isolated elevations of transaminases or bilirubin have been observed in patients with CF treated with Trikafta. In some instances, transaminase elevations have been associated with concomitant elevations in total bilirubin and/or the international normalized ratio (INR) and have resulted in patients being hospitalized for intervention, including in patients without a history of preexisting liver disease. Please refer to the full prescribing information for the complete list of Warnings and Precautions associated with each modulator as well as additional safety data. Thank you for your time. And I would like to add just one correction that I noticed in the Magellan report. When it is discussing the ivacaftor dosing for the newest age group on the four to less than six months old, it should say greater than 5 kg, not less than 5 kg. Thank you. Any other questions, I am happy to answer them. Thanks.

Jordan Storhaug: Thank you, Lisa. Then we will be moving on to Kristin Dandurand, Chiesi USA.

Kristin Dandurand: Can you hear me okay?

Jordan Storhaug: We can, Kristen. Yeah, go ahead.

Kristin Dandurand: Thank you for the opportunity to present. I am going to present on Bronchitol. It is a mannitol inhalation powder for oral inhalation use. So as you mentioned just a few minutes ago, CF affects approximately 31,000 patients in the US, with the lung being the key organ affected. And despite the introduction of CFTR modulators, most patients still require mucoactive agents to target manifestations of lung disease. Roughly 70% to 90% of patients utilize mucoactive agents as part of their airway clearance regimen. Part of the 2019 CFF Registry Report and cleaning of the device and a need for a power source for the nebulizer. So Bronchitol powder contains a sugar alcohol, D-mannitol. It is a spray dried into particles of respirable size. It is indicated as add-on maintenance therapy to improve pulmonary function in adult patients 18 years of age and older with cystic fibrosis. The use: You use Bronchitol only for adults who have passed a Bronchitol tolerance test, and the dosing of Bronchitol is 400 mg. It is 10 capsules twice a day by oral inhalation that is administered via portable breath-actuated dry powder inhaler. The doses are taken in the morning and evening, with the later dose taking about two to three hours before bedtime. Prior to the prescribing of

Bronchitol, the BTT or the Bronchitol tolerance test must be administered and performed under the supervision of a healthcare practitioner who is able to manage acute bronchospasm or identify patients who are suitable candidates for the Bronchitol maintenance therapy. Contraindications are hypersensitivity to mannitol and the failure to pass the BTT. The efficacy of Bronchitol for the treatment of CF was evaluated in three 26-week randomized, double-blinded, controlled studies in patients with CF. Since time is running out pretty quickly, I am going to direct you to the package insert. This information is in there as well, but in trial 1 a statistically significant improvement in FEV1 of 51 mL was observed for Bronchitol with a 95% confidence interval of 6 mL to 97 mL with a p-value less than 0.05. In trials 2 and 3, the between-group difference in FEV1 change baseline was 68 mL, with a 95% confidence interval of 24 mL to 113 mL and 52 mL, which was a 95% confidence interval negative 3 mL to 107 mL. A post hoc descriptive analysis of the adult subgroups in trials 2 and 3 observed between-group differences an adjusted mean FEV1 of 78 mL. I will direct you again to the PI for the warnings and precautions and adverse events. The most common adverse reaction of greater than 3% was observed in 761 patients across trials 1, 2, and 3 were cough, hemoptysis, oropharyngeal pain, vomiting, bacterial sputum identified, pyrexia, and arthralgia. In conclusion, Bronchitol is a dry powder inhaler formulation of mannitol using a breath-actuated inhaler. It has demonstrated a statistically significant improvement in FEV1 and CF-303 pivotal trials with consistent pulmonary function improvement in adults across these three studies. Maintenance of lung function in CF patients is the key focus of their care and patients often use multiple inhaled agents as part of their airway clearance regimen.

Jordan Storhaug: All right. Thank you, Kristin.

Kristin Dandurand: Thank you.

Jordan Storhaug: All right. I don't know if I see anybody else. Leta will confirm that for me, and then we can move on to the motion.

Leta Evaskus: This is Leta. I don't see any other hands raised.

Marissa Tabile: This is Marissa. Can you see the motion okay, Jordan?

Jordan Storhaug: I can now, yeah. Thank you.

Marissa Tabile: Okay, great. I think it is a little laggy.

Jordan Storhaug: Yeah.

Leah Marcotte: This is Leah Marcotte. I move that all products in the drug classes listed on slide 2 are considered safe and efficacious for their medically accepted indications and are eligible for the preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All non-preferred products require a trial of at least two preferred products with the same indication before a non-preferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Diane Schwilke: This Diane Schwilke. I second.

Jordan Storhaug: All in favor, please say. "Aye."

Multiple speakers: Aye. Aye. Aye. Aye.

Jordan Storhaug: Any opposed? All right, thank you. Next up for our topics is the Anticoagulants: Factor Xa and Thrombin Inhibitors. And back to you, Umang, for the presentation.

Umang Patel: Perfect. Thank you. Alrighty, so the next will be anticoagulants, specifically Factor Xa and thrombin inhibitors, just focusing on oral medications for these. On the next slide here. Perfect. There we go. Thank you. So a little bit of background, the first being venous thromboembolism. So VTE manifests as a deep vein thrombosis and a pulmonary embolism and is a major consequence of varied surgical procedures and medical conditions. DVT occurs when a thrombus composed of cellular material bound together with fibrin strands forms in the deep venous portions of the extremities most commonly the legs. The exact number of patients impacted by DVT and PE is unknown. However, it is estimated that these conditions affect approximately between 300,000 and 600,000 people in the US every year. If left untreated, approximately a third of patients who develop a PE will die within the first few hours of the event. Generally, the risk of VTE increases with the number of risk factors present, major traumas, and age. Due to the risk of morbidity and fatal PE associated with DVT, prophylaxis has become the standard of care for patients at high risk of thrombosis. And then CAD or coronary artery disease and PAD, peripheral artery disease, occurs in approximately 14

million Americans for CAD and 8.5 million over the age of 40 for PAD. Prevention and treatment of atherosclerosis focus on modifiable risk factors. Therapy includes lifestyle changes in the medical treatment of hypertension, hyperlipidemia, and diabetes. Antiplatelet medications such as aspirin, clopidogrel, prasugrel, ticagrelor, or vorapaxar are indicated for the reduction of thrombotic CV events in patients with established CAD or PAD. On the next slide, atrial fibrillation is a common arrhythmia ranging in prevalence from 2% in patients under 65 years of age to 9% for those 65 and older. The prevalence is higher in men than women, and it increases with age. And more than a third of patients with atrial fibrillation are 80 years of age or older. Patients with atrial fibrillation can have a reduction in cardiac output resulting in pooling of blood in the heart, atrial thrombus formation, and potential systemic embolization. Ischemic stroke is the most frequent clinical manifestation of atrial fibrillation-associated embolization, and it increases the risk of stroke five-fold. In patients with atrial fibrillation, the ACCP recommends measuring thromboembolism using the CHA2DS2-VASc score, which considers risk factors such as gender, age, history of stroke, TIA, thromboembolism, as well as history of CHF, hypertension, diabetes, vascular disease, PAD, or aortic plaques. The score ranges from zero to nine, with higher numbers indicating more risk. Guidelines for atrial fibrillation are over a year, so they are in the appendix, as well. On the next slide, here we have the AHA/ACC for the 2020 guidelines in the ACC 2020 guidelines, as well. These were right on the cusp of being about a year. So I kept these in here to err on the side of caution. The AHA/ACC in 2020 published guidelines on the diagnosis and treatment of hypertrophic cardiomyopathy. Notable pharmacological recommendations include for symptomatic patients with left ventricular outflow tract obstruction, non-vasodilating beta-blockers are recommended, but alternatives for select patients include verapamil, diltiazem, and disopyramide. For nonobstructive hypertrophic cardiomyopathy with preserved left ventricular ejection fraction, beta-blockers and verapamil and diltiazem are recommended in consideration of anticoagulants as the default treatment option for patients who also have atrial fibrillation independent of their CHA2DS2-VASc score, and additional guidance on the use of antiarrhythmic therapy and heart failure agents is included, as well. The ACC published an expert consensus decision pathway on managing bleeding episodes in patients taking oral anticoagulants. It updated the 2017 decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. They provide guidance for temporary or permanent interruption of therapy, general approaches to bleeding management, decision support for treatment with a

reversal agent, and indications and timing for reinstituting anticoagulant treatment. The panel does not recommend routine administration of platelets for patients on antiplatelet agents for major bleeding, and they do not recommend routine oral anticoagulant reversal for nonmajor bleeding, but clinicians may interrupt therapy until the patient is clinically stable and hemostasis is achieved. On the next slide here, moving to drug-specific. First, we have Pradaxa. In June 2021, FDA approved Pradaxa for the treatment of VTE and to reduce the risk of VTE in pediatric patients three months old or older. Previously, it was only approved for these indications in adults. Additionally, they also approved a 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg oral pellet pack for administration with select soft foods such as baby rice cereal, water, mashed carrots, bananas, applesauce, or apple juice. The oral pellets are indicated for the treatment of VTE and to reduce the risk of VTE in said pediatric patients three months to less than 12 years of age. As you can see, there are Blackbox warnings with anticoagulants, specifically premature discontinuation leading to thrombotic events and possible epidural or spinal hematoma in patients who have been treated with Pradaxa and are receiving neuraxial anesthesia or undergoing spinal puncture. As you can see, the dosage here is stratified by age, and the availability was updated to include the oral pellets, as I mentioned, for the pediatric patients earlier. In terms of special populations, first, patients who are pregnant, there is insufficient data to determine drug-associated risk in patients who are pregnant, and for patients with renal dysfunction, there have not been clinical studies completed for pediatric patients with a GFR of less than 50. On the next and final slide for this subclass, we have Xarelto. In December 2021, the FDA approved a new oral suspension formulation 1 mg/mL once reconstituted. And additionally at the same time, the FDA approved two new indications: 1.) The treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years of age and, 2.) For thromboprophylaxis in pediatric patients two years or older with congenital heart disease after the Fontan procedure. As you can see, Xarelto has a litany of other indications as well but just highlighting the two updates there. Dosage, as you can imagine, is broken down by indication and age as well, and the availability. No changes aside from the new oral suspension as well. Due to space in that one -- I just wanted full transparency -- or due to space, I was not able to include some of the other information such as a Blackbox warning, things like that. But please note that Xarelto also contains similar Blackbox warnings to Pradaxa, specifically with premature discontinuation and spinal epidural hematoma. I will go ahead and pause right there for the Committee.

Marissa Tabile: Hi, this is Marissa, I will go ahead and display the AHPDL. So the class that Umang just presented will be on line 12 here, which is the Factor Xa and thrombin inhibitors. And I will go ahead and pause and let you take a look at what we have preferred and nonpreferred on our AHPDL. And if we have any stakeholders and the motion, just whenever you are ready, Jordan.

Jordan Storhaug: Sure, we do have one stakeholder for this one. That is Piao Ching with Pfizer, so we can be ready at this time if you are ready to present.

Piao Ching: Good afternoon, my name is Piao Ching, and I am a pharmacist with Pfizer Medical Affairs. Thank you for allowing me to provide medical information on apixaban; the brand name Eliquis. For more information beyond what I present today, please refer to the package insert for the product, or I can provide further information upon request. We are asking the Committee to consider retaining Eliquis as a preferred option on Apple Health PDL. We have presented the relevant information contained in the prescribing information to the Committee before, so today I will provide new data published in December 2020. This is an independently nonindustrial study funded by the FDA. Using the FDA Sentinel Distributed Database, a retrospective cohort analysis compared the rates of ischemic stroke, gastrointestinal or GI bleeding, and intracranial hemorrhage (ICH) among adult [indistinct] patients 21 years and above initiating apixaban or warfarin between December 2012 and June 2018. The use of one-to-one propensity score matching (PSM) resulted in 55,038 apixaban/warfarin matched pairs. Subgroup analysis by age 21 to 64 years old, 65 through 74 years old, and 75 years and above were also conducted. There are several limitations which include the inability to include some data partners within the Sentinel System due to model convergence issues. Despite the use of a Propensity Score Matching or PSM, there is potential for this residual confirming due to unobserved confounders. Also, the year of cohort entry was not included in the propensity score model, and so the effect of [indistinct] trends within each ICD era might not have been accounted for. The analysis only includes patients receiving apixaban 5 mg twice daily. In the overall population, apixaban use was associated with a lower risk of ischemic stroke, GI bleeding, and ICH compared with warfarin. The same findings were observed in the 75 years and above age subgroup. In a 21 to 64 years of age subgroup, apixaban use was associated with a lower risk of ischemic stroke and GI bleeding and a similar risk of ICH compared with warfarin. In a 65 to 75 years age subgroup, apixaban use was associated with a similar risk of

ischemic stroke in ICH and a lower risk of GI bleeding compared to warfarin. With this in mind, we respectfully request that the Committee consider retaining apixaban as a preferred option on the Apple Health Medicaid PDL. Thank you very much for your time and attention. I will be happy to address any questions you may have.

Jordan Storhaug: Thank you. So if we have any questions, let us know. That is the only stakeholder that I had listed, and I don't see anybody with their hands raised right now. The next thing that we will do is take a look at the motion.

Laura Beste: Actually, this is Laura Beste. And I did have a really quick question here. Oh, so this is only oral. So injectable medications would be reviewed separately. Is that correct?

Marissa Tabile: Hi, this is Marissa. So Laura, a lot of our injectable medications that we have -- I would have to double-check with our injectables -- we either don't include them on the PDL, or they might be an archive class that we have reviewed pretty quickly in the past. But that is typically how we handle those injectable or IV medications. It may not be reviewed because it is not included on our PDL, or it is archived is usually the reason. But, yes, they would be reviewed separately if it was on the PDL.

Laura Beste: Okay, I just wanted to ensure that we weren't saying they could not be used or something by voting on this, so. Okay, thank you.

Marissa Tabile: No problem.

Kavita Chawla: This is Kavita Chawla. I move that all products in the Anticoagulants : Factor Xa and Thrombin Inhibitors oral drug class are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. All non-preferred products require a trial of at least two preferred products with the same indication before a non-preferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Laura Beste: This is Laura Beste. I second the motion.

Jordan Storhaug: All in favor, please say, "Aye."

Multiple speakers: Aye. Aye. Aye. Aye.

Jordan Storhaug: Any opposed? All right, the motion passes. So we are scheduled for a break on the next thing on the agenda, but we are running a little behind. Do you want to take that 10-minute break and come back?

Leta Evaskus: This is Leta. Yeah, I think it would be good to take a 10-minute break. So let's come back at, let's see. It is 3:11, so at 00:21 after. I will put up a sign.

Donna Sullivan: [Audio cuts out] Or come back at 00:20. Take a 9-minute break. How is that?

Jordan Storhaug: Yeah.

Leta Evaskus: Okay.

Jordan Storhaug: That sounds good to me.

Donna Sullivan: All right. Thanks.

Leta Evaskus: Marissa, if you could put up a sign that we will be back at 3:20. Oh, okay. I will do it.

Marissa Tabile: Sorry. I was trying to get myself off mute. I will go ahead and do it.

[short break]

Jordan Storhaug: All right, looks like it is time for us to get restarted again. Antidiabetics is our next topic here and Umang to start again for us. And thanks, Umang, for working on your volume. It has been a lot better for me at least.

Umang Patel: Awesome. I am glad to hear. Thank you. Next up, we will move on to antidiabetics. This will encompass both amylin analogs, SGLT2 inhibitors, DPP4 inhibitors along with DPP4 and SGLT2 inhibitor combos, DPP4 and TZD combinations, GLP-1, and GLP-1 insulin combinations. Moving on to the next slide, it is estimated that over 34 million Americans have diabetes, of which 90% to 95% have type 2 diabetes, and it is responsible for increased morbidity and mortality. Adequate glycemic control is crucial to minimize chronic microvascular and macrovascular complications. Exogenous insulin supplements deficient levels of endogenous insulin and temporarily restores the ability of the body to properly utilize carbs, fats, and proteins. Multiple

insulin proteins products are available and are used as replacement therapy and management of both type 1 and type 2 diabetic patients when glycemic goals are not met with oral antidiabetic agents. In addition to exogenous insulin, there are several pathways by which blood glucose may be regulated in diabetic patients. The SGLT2 inhibitors reduce renal glucose reabsorption in the proximal convoluted tubules, leading to increased urinary glucose excretion. On the next slide here, moving over to guidelines. Again, these were close to that one-year cut off so kept him in here to err on the side of caution. Additional guidelines are in the appendix. In 2020, the KDIGO guidelines came out for managing diabetes in patients with CKD. They recommend an individualized A1C target of less than 6.5% to less than 8% in diabetic patients with CKD. Based on CKD severity, macrovascular complications, comorbidities, life expectancies, hypoglycemia awareness and management resources, and hypoglycemic risk of medication. In addition to lifestyle therapy, KDIGO recommends first-line treatment with metformin and an SGLT2 inhibitor in most patients with a GFR of over 30 mL/minute. A GLP-1 agonist generally preferred DPP4 inhibitor, insulin, sulfonylurea, TZD, and/or AGI may be added as needed for glycemic control. These additions are guided by patient preference, comorbidities, EGFR, cost, and advice against the use of GLP-1 and DPP4 inhibitors. The ACC Guidelines in 2020 published an expert consensus decision pathway for CV risk reduction in patients with type 2 diabetes. They identify opportunities to initiate an SGLT2 inhibitor or GLP-1 agonist with demonstrated CV or renal benefit in patients with type 2 diabetes. A medication from either class may be initiated in any patient with type 2 diabetes and ASCVD at the time of diagnosis of type 2 diabetes or ASCVD or any time after diagnosis, including at hospital discharge. An agent from either class can also be started in patients with type 2 diabetes without established ASCVD but who are at high risk. In addition, initiation of an SGLT2 inhibitor with demonstrated CV or renal benefit is recommended in patients with heart failure and/or diabetic kidney disease. A GLP-1 receptor agonist is an alternative in patients with a GFR of less than 30. And then the American Gastroenterological Association came out with guidelines in 2021. They estimate that up to 70% of individuals with type 2 diabetes have nonalcoholic fatty liver disease. They informed that GLP-1/SGLT2 inhibitors and pioglitazone can improve the cardiometabolic profile and reverse steatosis in patients with diabetes and nonalcoholic fatty liver disease. They recommend a GLP-1 or pioglitazone in patients with indeterminant or high-risk clinically significant liver fibrosis. SGLT2 inhibitors appear to provide benefit in patients with nonalcoholic steatohepatitis (NASH) and associated comorbidities and the guideline

advice to prescribe a GLP-1 and SGLT2 inhibitor according to the ADA Guidelines. On the next slide, the ADA guidelines came out with a little bit of an update in 2021. As you can see, there is a lot of information here. I will just go over the main clinical updates found in bold. In patients using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal is a timing range of over 70% with a time below the range of less than 4%. During pregnancy, the ADA recommends a target A1C of 6% to 6.5% to be reasonable but can be adjusted based on hypoglycemia risk. More frequently such as monthly A1C monitoring may be required. For diabetes technology, an automated insulin delivery system should be considered in adults with type 1 diabetes who have the skills to use the device in order to improve time in range and reduce A1C and hypoglycemia. Systems may also be useful to improve glycemia in children. Regarding obesity management, the guidelines state that lorcaserin should no longer be used as the FDA requested its market withdrawal. For type 2 diabetes pharmacologic therapy, the guidelines advise to interrupt SGLT2 inhibitor therapy before scheduled surgery to avoid diabetic ketoacidosis. And this aligns with the label revisions for the SGLT2 inhibitors. And for management of CVD in patients with type 2 diabetes, the ADA advises to consider an SGLT2 inhibitor in patients with heart failure with reduced ejection fraction to reduce the risk of worsening heart failure and CV death. On the next slide here, we will move over to the drugs specific information. First, we have for Farxiga. In May 2021, the FDA approved a new indication to reduce the risk of a sustained EGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. As you can see, this medication has other indications. No changes in the other indications, precautions, dosing, or formulations. Regarding specialized populations, safety and efficacy have not been established in pediatric patients. It is not recommended in women who are pregnant during their second or third trimester. In terms of hepatic impairment, there is no dose adjustment recommended for mild, moderate, or severe hepatic impairment. And a GFR of less than 45 mL/min is not recommended to use this medication. On the next and final slide, we have Bydureon and Bydureon Bcise. And in July 2021, the FDA approved this medication as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes to include pediatric patients 10 years of age or older. Previously, it was only approved in adults. Again, similar to the previous slide, there are no other updates, no changes to the precautions. The Blackbox warnings are lined out in front of you. The dosing or formulations. In terms of special populations, it is not studied in patients with acute or chronic hepatic

impairment, and it is not recommended in patients with a GFR of less than 45. Go ahead and pause there for the Committee. [cross-talk] --

Marissa Tabile: Hi, this is Marissa [cross-talk] --

Umang Patel: Marissa, I apologize. I am going to keep going right through the insulins.

Marissa Tabile: That's okay. Yeah, I was just going to let the DUR Board know that we lumped all the antidiabetics into one motion. So I will just go ahead and have Umang do the rest of the clinical review, and then the motion will be at the very end.

Umang Patel: Thank you. Sorry about that. I was so excited to get a sip of water that I forgot. I will keep going. So we will move right along to the antidiabetic insulins. Here we have intermediate-acting, long-acting, premixed, rapid-acting, and short-acting. On the next slide here, we have the medication Semglee. In July 2021, the FDA approved Semglee as an interchangeable biosimilar to Lantus. It is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes and adults with type 2 diabetes, and it is not recommended for treating diabetic ketoacidosis. Everything here, as you will see, with precautions and dosing formulations is identical to Lantus. For precautions, you as the Committee can imagine with insulin one of the precautions is hyperglycemia or hypoglycemia may occur with changes in insulin regimen. Hypokalemia can occur and fluid retention and heart failure with concomitant TZD use. Dosing, as you imagine, for insulin is very individualized, and the formulations are an injection of a U-100, so 100 units/mL, and they are available in 10 mL multiple dose vials and a 3 mL single-patient-use prefilled syringe. And now on the next slide here we have Rezvoglar. I apologize for my mispronunciation there if I mispronounced it. In December 2021, the FDA approved the second biosimilar insulin to Lantus. It is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes and adults with type 2 diabetes. Again, to not, I guess, repeat myself here, you can see there are identical limitations of use, identical precautions, dosing is identical as it is individualized, and the formulations are available in a 3 mL single-patient-use prefilled syringe. I will go ahead and pause here now for the Committee.

John MacKay: Umang, I have a question for you. Is Bydureon available in the marketplace currently?

Umang Patel: That is a great question. I am going to look into that to see if there is an active recall.

Donna Sullivan: Hi, Umang. This is Donna. I think it is just the by Bydureon Bices, right? Is that correct, is available?

John MacKay: That is from [cross-talk] for my wholesalers. I just noticed that it was preferred as was one of the GLP-1 agonists and not available in the current marketplace.

Jordan Storhaug: And Donna is correct. It is only Bydureon Bices, not Bydureon.

Donna Sullivan: So we can get that removed. This is Donna. We can get that removed from the PDL document.

Marissa Tabile: Hi, this is Marissa. I am sure you guys can see here is all of the preferred and nonpreferred for the antidiabetics that Umang just reviewed. I will try to go through them slowly. If you have any questions, please let me know.

Jordan Storhaug: We will try to be scrolling through that, but we do have a couple of stakeholders as well. So first up is Mark Maneval of Boehringer Ingelheim.

Mark Maneval: Awesome. Thank you, very much. Can you hear me?

Jordan Storhaug: I can. Go ahead.

Mark Maneval: Awesome. Good afternoon. And thank you for giving me an opportunity to speak with you today. My name again is Mark Maneval. I am a Washington state-based pharmacist and Health Economics and Outcomes Research Liaison for Boehringer Ingelheim. I am pleased to provide you today with an update on our product line containing the SGLT2 inhibitor, empagliflozin. Jardiance, Synjardy, Synjardy XR, Glyxambi, Trijardy XR are all indicated adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes. Empagliflozin, a component of Synjardy, Synjardy X-RAY, Glyxambi, and Trijardy XR is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease. Jardiance is also indicated to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure with reduced ejection fraction. The US FDA has accepted our supplemental new drug

application and granted priority review for Jardiance tablets for adults with heart failure independent of left ventricular ejection fraction. According to the FDA, a priority reviewed designation is intended to direct overall attention and resources to the evaluation of applications for a treatment that, if approved, would be a significant improvement in the safety or effectiveness of treatments for serious conditions. The supplemental new drug application is based on results from our EMPEROR-Preserved trial, which has the potential to establish empagliflozin as the first therapy to show statistically significant improvement in heart failure outcomes in adults with heart failure with preserved ejection fraction. You may recall that the FDA also granted breakthrough therapy designation back in September of 2021, which underscores the critical need for a clinically proven treatment for people with this highly prevalent debilitating condition. We expect a decision from the FDA in the first quarter of this year in 2022. Jardiance is not indicated for heart failure in adults with heart failure and with preserved ejection fraction. Jardiance is not recommended in patients with type 1 diabetes. It may increase the risk of diabetic ketoacidosis in those patients. Jardiance is not recommended for use to improve glycemic control and adults with type 2 diabetes with an EGFR less than 30. Jardiance is likely to be ineffective in this setting based upon its mechanism of action. Thank you for your time today. I am happy to answer any questions you may have.

Jordan Storhaug: Thank you so very much. The next one is Nicole Ehrhardt, UW Diabetes Institute.

Nicole Ehrhardt: Good afternoon. Can you hear me?

Jordan Storhaug: Yeah [cross-talk].

Nicole Ehrhardt: My name is Nicole Ehrhardt, and I am one of the adult endocrinologists at The Diabetes Institute. And I am really excited to be here to talk about this important topic, which is making the weekly GLP-1 receptor agonist as a preferred GLP-1 receptor agonist on the formulary. That includes some semaglutide 0.25 mg to 1 mg and hopefully 2 mg soon, and dulaglutide 0.75 and up to 4.5. And so why is it so important? Well, I think you saw in our letter that we highlighted earlier and sent you in the week about how important this topic is because I had over 18 endocrinologists in just 24 hours sign on to these sentiments. So why do we want to use the weekly receptor agonist as our preferred GLP-1 agonist? Well, first to point out, we know there is a cardiac benefit to these medications. And right now one of

the GLP-1 receptor agonists that you have on the formulary does not have the cardiac indication. So that is by Byetta or Bydureon or exenatide, which you probably also know is a twice-a-day medication, but what you may not know it also has some time to the meal. And so you have to time at 30 to 40 minutes before the meal to get the full effects, which is also very burdensome to the patients. So we would ask that exenatide be removed from the formulary, and one of the weekly GLP-1 receptor agonists add as the preferred medication. Additionally, what we know is that the A1C lowering, the weight loss potential is greater for the weekly GLP-1 receptor agonist, which I also detail in the letter. And finally, I think this is a little less data, but truly what I see with my patients every day is that we also know that the American Diabetes Association tells us that we should use the GLP-1 receptor agonist as a first-line injectable, so over insulin now, and that came out in the guidelines from 2021. However, what I think is less tangible and people don't understand is that when I tell people you are going to be on an injectable, their face falls. They [indistinct] it with insulin even if it is not insulin, and they feel they failed with their diabetes. You give them a weekly GLP-1 receptor agonist, and you tell them it is going to cause them to lose weight, it is going to work great for their diabetes, and it is going to have heart benefit, and they are empowered to work on their diabetes, and we just see the results. And so I will end with a story about a patient. So I just saw a patient last week, who six months ago we switched from liraglutide, which is Victoza, your other preferred GLP-1 receptor agonist on the formulary, to semaglutide. He also was on metformin but 160 units of insulin. Six months later, he has lost 30 pounds, he is down to a cumulative dose of insulin of 40 units, and his goal is to lose 20 more pounds and get off of insulin. Now, this might be an exceptional case, but I see every day the benefit of the weekly GLP-1. So we would ask that semaglutide and dulaglutide be added to the formulary preferred without prior authorization after metformin if clinically indicated. Thank you so much for your time.

Jordan Storhaug: Thank you. And lastly, we have Sarah Villarreal, Novo Nordisk.

Sarah Villarreal: Hi. Can everyone hear me?

Jordan Storhaug: We can hear you. Go ahead.

Sarah Villarreal: Perfect. So my name is Sarah Villarreal, and on behalf of November Nordisk, I would like to provide a few updates on semaglutide injection branded Ozempic, which as I mentioned earlier, is a once-weekly GLP-1 receptor

agonist. It was approved by the FDA in December of 2017, and it is the most recently approved weekly GLP-1 receptor agonist. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. And as of January 2020, it gained a new indication to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. This places it in the elite class of GLP-1 agents recommended by the ADA for patients with type 2 diabetes at high cardiovascular risk, which typically consists of around 20% of the patients. This FDA decision was based on the combined data sets from the SUSTAIN-6 trial with Ozempic, which showed a 26% relative risk reduction in MACE events, and the PIONEER 6 trial with oral semaglutide brand name Rybelsus showing a similar reduction of 21%. Thus adding Ozempic to join Victoza as a preferred formulary agent, provides daily and weekly GLP-1 options, both with an indication to reduce cardiac events. In addition, we now have a new Ozempic Pen containing 4 mg or 3 mL delivering a full months' dose in a single pen versus the previous two-pen pack, each with 2 mg. Besides these new features, what has always made Ozempic stand out within the GLP-1 class is its efficacy in achieving glycemic targets as well as lowering body weight. In regard to efficacy, in head-to-head trials, which were 30 to 56 weeks in duration, Ozempic 0.5 mg demonstrated reductions from 1.2% to 1.5%, and Ozempic 1 mg dose demonstrated A1C reductions from 1.4% to 1.8%. While not indicated for weight loss, the weight effect was a secondary endpoint in the sustained clinical program. Mean weight loss of 7 to 10 pounds was noted with a 0.5 mg dose of Ozempic, and mean weight loss of 10 to 14 pounds was seen with the 1 mg. Two head-to-head trials comparing Ozempic to other once-weekly GLP-1 agents have been published, sustained three compared Ozempic to Bydureon, and sustained seven compared Ozempic to Trulicity. Both trials demonstrated that therapy with Ozempic resulted in greater A1C reductions, a greater percentage of patients achieving A1C targets, and a greater weight loss versus both competitors. GI side effects including nausea, vomiting, diarrhea, abdominal pain, and constipation are the most commonly reported adverse events with Ozempic. Similar to other long-acting GLP-1receptor agonists, there is a boxed warning with Ozempic regarding the potential risk of thyroid C cell tumors. And as such, patients with a personal or family history of MTC and patients with MEN2 should not use Ozempic. For additional safety information, please refer to the package insert. And I would also like to thank you for your consideration. And I will take any questions.

Jordan Storhaug: Thank you very much. I was just checking to see if we have any other stakeholders, of which I don't see any. And we could then go to the motion.

Leah Marcotte: Jordan, could we just clarify the preferred? Marissa, you had gone through the table pretty quickly. I had a hard time keeping up with the preferred versus non-preferred and also the general rule. I know the generic names very well and the brand names less well, so if there is any chance we could include your generics on this table, it would be really helpful. But is there a once-weekly GLP-1 agonist that is accessible? Just that the data on these medications is so good and having it accessible, I think, would be really helpful.

Marissa Tabile: Hi, this is Marissa. So, Leah, I will take that into consideration for the next PDL. Thank you for that feedback. So here are the GLP-1 agonists. It starts on line 40. We do not have a preferred once-weekly product, but we did create a policy, which just went into effect February 1, which would require patients to step through either Byetta or Victoza. Those are our two preferred options right now. But of course, we would review things on a case-by-case basis. If one of those agents is not appropriate for them, it could still be approvable if a once-weekly is more appropriate for them. And that is based on clinician discretion.

Leah Marcotte: Okay, so it sounds like right now where liraglutide is available as preferred but would need prior auth for semaglutide or any of the once-weekly dosing.

Marissa Tabile: That is correct.

Leah Marcotte: Okay.

Kavita Chawla: Hi, this is Kavita Chawla here. So along these lines are there any steps that we can take as the P&T Committee to make semaglutide or dulaglutide as preferred agents because they have such overwhelmingly positive benefits for the patients without having to go through that barrier of a pre-auth process?

Leah Marcotte: And one additional question is, there was a recent head-to-head trial of liraglutide and semaglutide, and semaglutide did have pretty significant clinical benefits over liraglutide. I don't think we have been able to review that study, and so I don't know if that evidence has been taken into consideration on the [indistinct] yet.

Marissa Tabile: This is Marissa. Hey, Donna, did you have any feedback on that? I think Vita was wondering if the DUR Board had any. Sorry, Kavita. If you wanted to go ahead and repeat your question. [cross-talk]

Kavita Chawla: Sure. Yeah, Kavita here. Just wondering if we as the DUR Board have an ability in the phase of really compelling clinical efficacy evidence to propose either semaglutide or dulaglutide, especially semaglutide as a preferred agent for the Apple PDL.

Donna Sullivan: So this is Donna. So the recommendations, the motions that you make as a DUR Board are our recommendations. The reason why these drugs are not preferred is the fact that they are so much more expensive than the daily product that we have not made them preferred and wide open. We would love for manufacturers to sharpen their pencils and give, provide more meaningful discounts on these drugs so that they are more affordable for the program and sustainable to have them as open access. So at this time, I would not be inclined to add one because they are truly, significantly more expensive. We are talking -- and it is not just $50. It is several $100 to $1,000 more. I would have to look at the actual costs to give you relativity, and I don't have that information in front of me, but it is significant.

Laura Beste: And Donna, this is probably an ignorant question on my part, but remind me. So if they are a preferred status, they can be prescribed and received by the patient without prior authorization, is that correct?

Donna Sullivan: In most cases, yes.

Laura Beste: Okay.

Donna Sullivan: So if it does not say prior auth required in column F, then they do not require prior authorization. Some drugs are in other classes. We have created them. We call them preferred, but we still require prior authorization to make sure they are being used as indicated, but not for these particular classes.

Laura Beste: Thank you. And I see that column now. Sorry, I missed that. That is why you have that right there. And so liraglutide right now should be able to be prescribed without prior authorization?

Marissa Tabile: This is Marissa. Yes, that is correct. That is Victoza for your reference.

Jon MacKay: This is John Mackay. So if Bydureon is not available on the marketplace, would it be possible to at least make once weekly GLP1 available? Change the Bydureon Bices to preferred?

Donna Sullivan: Yeah, that is the one that is really expensive.

Jon MacKay: Oh, besides, I mean, that is not my preferred agent go to, but I feel in terms of adherence issues that we need at least one weekly.

Donna Sullivan: Yeah. They are all crazy expensive compared to [cross-talk] doses.

Diane Schwilke: This is Diane Schwilke. I would not advocate for that one because it is one of the three that does not have any cardiovascular benefit proven. Yeah, it would need to be one of the others if we were going to require some sort of weekly, either Trulicity or Ozempic. And Ozempic head-to-head with Trulicity most recently saw we had better weight loss as well as A1C reduction.

Laura Beste: This is Laura Beste. So just from an education standpoint, how long do they have to be on the daily agent prior to failing that therapy? I mean, is there a three-month window? What is the expected trial period? Or is that documented somewhere?

Marissa Tabile: Yeah, this is Marissa. So part of our GLP-1 policy, of the trial would be 90 days, so three months.

Laura Beste: Okay.

Kavita Chawla: Kavita here. Marissa, would you please remind us? So what is the definition of failure? Is it a lack of A1C improvement? Is it intolerance? Or is it also nonadherence for the patient?

Marissa Tabile: This is Marissa. I don't know if in the policy -- sorry, I am trying to reference it. I believe it would just be like no clinical benefit. So it would probably be no reduction in A1C. Actually, here we have it. "History of failure" is defined as the inability to achieve glycemic control, intolerance, or contraindication, or clinically inappropriate to that particular agent.

Kavita Chawla: Kavita [cross-talk].

Marissa Tabile: Are we able to make -- oh, go ahead. Sorry, Kavita.

Kavita Chawla: No, no. Sorry, it was because there is such a major overlap between diabetes and obesity, I cannot remember whether there is a separate class of anti or obesity management drugs that we would review at a separate time? And maybe I am just thinking of failure to improve in my mind also often includes the weight components, and metabolic syndrome is all of the above? So I guess the question is, is there a different class of anti-obesity medications that we would be reviewing at some point later this year, where this could be brought up for discussion again?

Marissa Tabile: Yeah. So Kavita, this is Marissa. We actually don't cover any weight loss medications for the Apple Health Program. So those products, I don't believe they are even included on our PDL, but we don't cover any weight loss medications for Apple Health. So it would not be reviewed at any DUR Board meeting.

Leah Marcotte: Is there a way that we could make a recommendation pending more cost-effective options? We think that the once-weekly dosing of the GLP-1 agonist is compelling from a clinical standpoint and our clinical outcomes standpoint. And pending some reduction in cost, we would strongly recommend that they be added and be reviewed at some point. I don't know if there is any wording there that we can at least signal that these medications are really effective while understanding the cost implications.

Donna Sullivan: You can add that if you want to the motion. I mean, obviously, if the cost comes down and they get closer in price, we will definitely want to add it. This is kind of our leverage to be able to get manufacturer rebates is through the PDL. So that is kind of the challenge that we have to face. Okay. And we only have five minutes left in the scheduled meeting. So are you ready to make a motion?

Laura Beste: This is Laura Beste. I want to ask one more question. Is there any way that they can add restrictions to them for patients who have a high cardiovascular risk so that you could restrict them and use them first-line for patients who have that high cardiovascular risk that would definitely benefit from that over the other agents?

Donna Sullivan: And hi, Laura. This is Donna. Yeah, and we can look into something that. We have done that in the past for Ramipril back when Ramipril was expensive. But yeah, we can take that away and try to see if we can come up with some.

Laura Beste: Because it just seems there is a real benefit for this class of medications for a certain part of the patient population that would significantly benefit. So some of the patients might be okay with the once-daily, especially if there is a significant cost difference. But for those patients who have that high cardiovascular risk, this would certainly be the preferred agent over the preferred ones that are on the formulary currently. So if they could have them maybe restricted. I don't know if that is an option, but that might be a way to at least make it a little more preferable as an option.

Jordan Storhaug: All right. A couple of things, I guess. This is Jordan Storhaug. On the motion, I don't see anything in our motion that necessarily would require there to be two preferred products of each drug class, or as it has been redefined a sub drug class, and it seems like, technically, I think, right now, you could have two types of insulins that we need the way that it is written right now. So I wonder if that should be included somewhere.

Marissa Tabile: Hi, this is Marissa. So Jordan, sorry, was there something you would like me to add to the motion?

Jordan Storhaug: I am trying to figure out my language for that. So there should be two preferred drugs from each antidiabetic subclass.

Donna Sullivan: Hi Jordan. This is Donna. [indistinct] Are you trying to say you want two preferred drugs from each drug class? Or are you commenting on that you must try and fail two preferred drugs within a drug class?

Jordan Storhaug: No. My comment was not necessarily for that one. My comment with that was just right now it is such a huge class, and I would want to make sure that there is a preferred GLP-1 agonist and there is a preferred SGLT2 inhibitor, and I don't think we have anything right now that says that.

Donna Sullivan: Okay, so you want to say something like there should be at least one preferred drug within each subclass [cross-talk] of antidiabetics.

Jordan Storhaug: Yes.

Diane Schwilke: And I would also want it to include "with cardiovascular benefit" because not all within each subclass have that. So if it is an option, I would want that to be preferred. This is Diane Schwilke. Sorry.

Donna Sullivan: This is Donna. I would push back a little bit on that. We can make it preferred, but it would still be on prior authorization, which basically means it is still nonpreferred if we are only going to limit the weekly medications to those with high cardiac risk. So if you want to say, make drugs with cardiac benefit available to those at high cardiac risk or something of that nature.

Diane Schwilke: Well, I think you could argue that any, especially poorly-controlled diabetic, is inherently going to have cardiac risk.

Donna Sullivan: Right.

Kavita Chawla: Kavita here. I guess the way I am reading this right now, "all nonpreferred products require a trial of at least one preferred product in each antidiabetic subclass.

Donna Sullivan: Marissa, are you typing? I think you are changing the wrong part.

Marissa Tabile: Hi. This is Marissa. Yeah. I was trying to wordsmith it. If you guys want me to go to the part that you want me to correct, just let me know. I was trying to type and listen at the same time.

Donna Sullivan: Undo all the changes you just made. Okay. And then before the sentence, add a new sentence that says, "there must be at least one preferred agent in each antidiabetic subclass."

Marissa Tabile: And there must be at least one preferred product in each antidiabetic subclass?

Donna Sullivan: Yeah.

Marissa Tabile: Okay. Thanks.

Donna Sullivan: And then leave the last sentence the same.

Marissa Tabile: Okay.

Kavita Chawla: Kavita here. And I would add a subclass with proven cardiovascular benefit when applicable within our two classes here where there are agents that have proven cardiovascular benefit versus not or proven nephroprotective benefits versus not. So I don't know how detailed we want to get in here. But like the class example here beings exenatide is not really useful to have it as the only preferred. So it is good that we have liraglutide, but we want to make sure we retain that.

Susan Flatebo: This is Susan Flatebo. Do we need to get that detailed when the ordering provider probably knows this patient? And I would think would order the cardiovascular drug he would want for his patient. I don't know. I just feel we are going to get too detailed in this. I think it looks/sounds good how it is. I mean, how much direction do we really want to [cross-talk] there is some provider discretion.

Kavita Chawla: Kavita here. I thought that this is more for us as HCA, or this is more a direction for HCA to make sure that they are including a preferred medication in each drug class. It is not for the provider, but it is for HCA. Not HCA, sorry. DUR and Apple PDL to include at least one medication as preferred. Am I understanding that correctly?

Jordan Storhaug: I think the concern that Kavita is trying to talk about is if, for instance, so they were not able to get as good of a price on Victoza, and so that fell off of the PDL, then we would not have a GLP-1 agonist with cardiac proven benefit. And we want to make sure that there is one of the GLP-1 classes that have that cardiac benefit.

Marissa Tabile: Hi, this is Marissa. Sorry, Kavita. Can you repeat that? I didn't document it. I apologize.

Kavita Chawla: Kavita here. Yes. So just after subclass, comma, with proven cardiovascular and nephroprotective benefit where applicable.

Donna Sullivan: And I think I would like to go back then and look at the quality of the evidence on these. If we are going to get to this level of detail in deciding what makes something preferred because some of these are not. I mean, the cardiovascular is a primary outcome. I am not familiar with the data on the nephroprotective, so I am cautious to try to say we have to go find something that is nephroprotective if there is not strong evidence supporting its use, but it is something that is being advertised as [cross-talk] drug.

Kavita Chawla: Kavita here. Yeah, part, and then I think this is why KEDIGO included SGLT2 inhibitors as first-line because of that very reason of SGLT2 inhibitors specifically dapagliflozin and empagliflozin having those nephroprotective benefits that were majorly clinically significant, so more than advertising. It is also the national guidelines that are strongly recommending these. That was prompting me to include them there.

Donna Sullivan: And again, I would still want to go back and look at the evidence and potentially have DERP look at the evidence on these and get a good grading for it before we add the nephroprotective language in here.

Jordan Storhaug: Donna, do you have a suggestion for how to move forward with this?

Donna Sullivan: Yes.

Jordan Storhaug: Because I think [cross-talk] the Committee have been educated, I guess, about this benefit, and yet we haven't had it. I think, also, we had some of our presenters today bring up this, and yet we [indistinct]. I think there is some concern that when are we going to feel this again? And do we have a way of moving this forward?

Donna Sullivan: I mean, you can make the recommendation if you want. We will move forward with the cost analysis as we typically do.

Laura Beste: This is Laura Beste. Can ask one more clarifying question? So the next sentence says that they require a trial of at least two preferred products with the same indication before a nonpreferred drug will be authorized. So does that mean that if there are on GLP-1 they need to do three months of one product, three months of another before they can go to a nonpreferred agent? Is that correct? So would need to fail six months of the preferred?

Marissa Tabile: This is Marissa. So the way that we have it written in the policy is that they can be used separately or simultaneously with different agents for a minimum of 90 days. So if they were taking metformin and an SGLT2 inhibitor at the same time, it would just have to be 90 days for both of those. So they could be taking typically in diabetes, you will see patients on metformin, and I am just saying like insulin and then possibly other agencies, as well, all at the same time. So if we see that there is simultaneous use of

those, then we would qualify that at least for 90 days as a trial. It doesn't have to be [cross-talk] --

Laura Beste: But not within the same class.

Marissa Tabile: Yeah. It doesn't have to be separate 90 of this, 90 of this, 90 of this, all at different times.

Jordan Storhaug: I think Marissa for where, specifically, I think she is kind of talking about GLP-1s is that all physicians, I think, are going to prescribe Victoza first because it has the known cardiac benefit. You would need to try that for 90 days. You find that it fails. If you are not able to get your control there, at which point then you would need to move to Byetta, do 90 days of that to say that that failed, at which point then you would be able to try a different GLP-1.

Marissa Tabile: This is Marissa. So specifically for our GLP-1 policy, we do lay out that it is just metformin, one preferred SGLT2, and one preferred GLP-1, so it could be either Byetta or Victoza. But we do require also an SGLT2 inhibitor trial and failure as well as metformin. So it would be all three of those. And they could pick either Byetta or Victoza in reference to the GLP-1s. They don't have to try both, but as long as there is history of one of those on top of the other two agents that we laid out.

Jordan Storhaug: Okay.

Kavita Chawla: I guess I will move forward. I move that all products in the drug classes listed on slides 7 and 8 are considered safe and efficacious for their medically accepted indications and are eligible for preferred status and grandfathering at the discretion of HCA. Products in this class may require prior authorization to determine medical necessity. There must be at least one preferred product in each antidiabetic subclass with proven cardiovascular and nephroprotective benefit, if applicable. All nonpreferred products require a trial of at least two preferred products with the same indication before a nonpreferred drug will be authorized unless contraindicated, not clinically appropriate, or only one product is preferred.

Leah Marcotte: This is Leah Marcotte. I second that motion.

Jordan Storhaug: All in favor, please say. "Aye."

Multiple speakers: Aye. Aye. Aye. Aye.

Jordan Storhaug: Any opposed? All right. That gets that for that one. Do you guys want us to do the last set of agents tonight? Do you want to [indistinct] again?

Donna Sullivan: Hi, Jordan. This is Donna. We can go ahead and move that class to the next meeting or review it at a different time.

Jordan Storhaug: Okay. Well, with that then it was a little bit of a change, but it looks our business for today is done, and we can adjourn. Thank you.

Virginia Buccola: Thanks, Jordan.

Laura Beste: Thank you.

Diane Schwilke: Yeah. Thanks, all.

Leta Evaskus: Thank you, all.

Susan Flatebo: Thank you, Jordan.

Donna Sullivan: Thank you, everybody.

Kavita Chawla: Good evening.

[end of audio]