Curtis Harrod: Similar risk profile for overall adverse events and gave this a grading of moderate quality of evidence. However, for serious and discontinuation, because of adverse events, we rated this as low really based on curious imprecision, because we have fewer events here. So, we have wide confidence intervals, and that lowers our confidence in the findings, but again, we saw a similar finding with regard to there was no significant differences between these, alirocumab and ezetimibe, but lower quality of evidence.

So, if we can go onto slide number 17 now, we have evolucumab versus ezetimibe, in which we identified three eligible fair-methodological-quality randomized control trials. Study durations for these three trials ranged from 12 to 24 weeks. Sample size, overall, was 590 participants. We saw significant reduction in LDL levels for evolucumab versus ezetimibe. This ranged from 36% to about 38%. So, some homogeneity in those findings across the three studies. And we rated this as high quality of evidence. We saw no differences between evolucumab and ezetimibe for overall adverse events and again rated this as high quality of evidence. We have, however, see a lower risk for discontinuation as a result of adverse events in evolucumab versus ezetimibe. Again, this is different than what we saw in the previous study, in which we saw an increased risk with regard to a PCSK9 inhibitor for an adverse event. However, you see a 9.4% adverse event within evolucumab and 22% roughly in ezetimibe. So, this is a pretty meaningful reduction of about 57% evolucumab. We rated this evidence as moderate quality. And then, when we look at serious adverse events in cardiovascular events, we have comparable risk profiles. And we rated this as low quality of evidence. So, a little bit of a mixture on findings with regard to adverse events in these three studies.

When we go onto slide number 18, we have evolucumab plus ezetimibe versus ezetimibe alone, and we identified one fair-methodological-quality

randomized control trial on this topic. There is a 12-week study duration and a small sample of 64 participants. So, we saw significant reductions in LDL levels with evolucumab plus ezetimibe versus ezetimibe alone. This accounted for a 47% reduction of LDL levels. We rated this as low quality of evidence. Similar risk profiles for overall adverse events between these two groups. We rated this as low quality of evidence, as well. The were no additional outcomes that we identified that we could draw meaningful conclusions on.

So, transition out of slide number 19, and this is where we begin talking about key question number three. Those are for patients not achieving target levels of lipid lowering.

So, the transition now to slide number 20. We have alirocumab versus placebo. So, I've been talking about this a little bit. Now, we're finally getting into the, the meat of the findings here. So, alirocumab versus placebo was evaluated in a very large multicenter double-blind randomized control trial. Study duration for this large trial was 34 months. Alirocumab was administered between 75 mg and 150 mg and was compared to a placebo. You can see that's close to 19,000 participants with acute coronary syndrome, and this occurred from one month to 12 months earlier, were eligible for the studies. They had an additional eligibility criteria, and that was LDL levels of 70 or greater mg/dl, and this is despite high-intensity statin therapy. So, for findings, we see a significant reduction of cardiovascular events with alirocumab versus placebo. So, we do have a GRADE rating on this profile, because it was a late-breaking study when we were doing the systematic review, and we wanted to provide it in the review for DERP's benefit. However, it would be comparable to our other cardiovascular disease study, and I will get to that in the subsequent slide. So, that's evolucumab. Going back to alirocumab versus placebo, we see a 9.5% reduction in the alirocumab group and 11.1% reduction with placebo group. So, to belabor my point, this is a small absolute difference, despite the relative significant difference observed with the hazard ratio. We observed fewer deaths with alirocumab, 3.5% versus 4.1%, and a comparable reduction of 15%. Similar deaths for cardiovascular causes was observed also in this study. So, we had 2.5% versus 2.9%, and this was not statistically significantly different.

So, we'll move on to slide #21, in which we have alirocumab versus other lipid-lowering regimens, which we identified three fair-methodological-quality randomized trials. The trials were all 24 weeks duration, and the sample was close to 1400 participants. What we see for our findings is a significant reduction in LDL levels with alirocumab versus other regimens. This ranged from 24% roughly to 49%. So, some heterogeneity there. Despite that, we're confident of high quality of evidence that LDL's are being reduced by alirocumab. We see a similar risk profile between these two groups for overall adverse events and rated that as high quality of evidence, as well. No additional meaningful conclusions could be drawn from other outcomes in this study.

So, we'll go on to slide number 22, in which we have alirocumab versus standard of care. We identified one fair-methodological-quality randomized control trial on this topic. It was 24 weeks, the study duration. The sample was 413 participants, and for our findings, we had significant reductions in LDL levels for alirocumab versus standard of care and accounted for a 43% reduction in LDL levels. We rated this outcome as moderate quality of evidence. For overall adverse events, it was not significantly different between alirocumab and standard of care and also rated this as moderate quality of evidence. There are no meaningful additional outcomes that could be assessed with GRADE in this study.

So, go on to slide number 23, and I have a few more before we get into question number four. So, evolucumab versus placebo, so this is the other very, very large trial analyzing cardiovascular diseases. This was incorporated fully within the DERP review with our GRADE ratings. So, this one good methodological quality study was evaluated over a 26 month period, so over two years, and had about 28,000 participants in the study. What they observed was significant reductions in cardiovascular events with evolucumab compared to placebo and comparable to what we've been talking about today, is despite a relative reduction, the absolute difference was quite small. We rated this as high quality of evidence. So, I alluded to this earlier with alirocumab, I would say our GRADE rating would be comparable to this in which we have high quality of evidence for reduction.

So, transitioning to slide number 24, with evolucumab versus ezetimibe, we identified one fair-methodological-quality randomized trial, had 12 week study duration and close to 2000 participants in the trial. Similar to other studies that you've heard me talk about today, they see a significant reduction in LDL levels. For this study, you see about a 44% reduction with evolucumab compared to ezetimibe, and the GRADE rating for this outcome was moderate quality of evidence. For overall adverse events, we see no significant differences between these two groups and rated this as high quality of evidence. Similar finding, as well, with serious adverse events and discontinuation of adverse events. We could not identify any additional outcomes in this fair-methodological-quality study that we would be able to draw meaningful conclusions on.

So, we'll transition out of slide 25, in which we're looking at mixed populations with PCSK9 inhibitors as adjunct or firstline therapy, so monotherapy or adjunct therapy.

On slide number 26, we have evolucumab plus standard of care versus standard of care alone, and we have one poor-methodological-quality pooled analysis containing two randomized control trials. This is a little bit under one year, as far as study duration, and close to 4500 participants were in the study. Again, a similar trend with LDL levels. We see a significant reduction of about 58% with evolucumab plus standard of care versus standard of care alone. We rated the outcome as moderate quality of evidence. For cardiovascular events, this was the other study that did analyze it in a meaningful way. We see a significant reduction with evolucumab plus standard of care versus standard of care alone, and we see a 53% reduction here. The confidence interval is pretty wide, ranging from about a 72% reduction to a 22% reduction. So, we downgraded for imprecision, as well as the poor-methodological-quality of the study and rated this as low quality of evidence. Continue on to adverse events, we see a significantly higher adverse event rate with evolucumab plus standard of care versus standard of care alone, so 69% with the evolucumab plus standard of care, and 65% roughly with the standard of care alone, so a minor increase. We rated this as moderate quality of evidence. For serious adverse events, we have low quality of evidence and did not see significant differences between the

two groups. We could not identify additional outcomes that we could draw meaningful conclusions on within the study, as well.

So, now, transition to slide 27, and this is our slide before I'll get into summary and conclusions. So, alirocumab versus ezetimibe was evaluated in one fair-methodological-quality randomized trial. The study was 24 weeks' duration with a sample of 103 participants. We saw significant reductions in LDL levels for alirocumab, and there is a typo on this slide. My apologies. We've only presented this report twice and evaluated it through editors twice, and I just happened to catch it last night when I was giving myself a rehearsal presentation. So, it says standard of care, but we mean ezetimibe. So, apologies for that error, but alirocumab versus ezetimibe, it was a 32% reduction there, and the GRADE rating for this outcome was low quality of evidence. We saw a lower risk for adverse events for alirocumab versus ezetimibe, and that was 69% to 78%. This was not a statistically significant difference, however. We rated this as low quality of evidence, as well. So, no meaningful conclusions on other outcomes could be drawn within this one fair-methodological-quality study.

So, we'll transition now to our summary findings here and then wrap up with conclusions and then take questions. So, on slide 28, the overview of the updated DERP systematic review is that we confirm findings from the original DERP systematic review in 2015. So, we found comparable findings between that and our update. We identified additional relevant evidence for non-familial hypercholesterolemia, and we identified two important trials that are analyzing cardiovascular events with PCSK9 inhibitors. That's the Fourier trial and the Odyssey Outcomes trial. We identified no eligible studies that had head-to-head evidence for one PCSK9 inhibitor versus another, as well as no evidence was identified analyzing the long-term benefits and harms of PCSK9 inhibitors.

So, we'll wrap up with slide 29 here with conclusions. So, overall, PCSK9 inhibitors are effective at treating LDL levels. They will reduce LDL levels significantly, and this is particularly in individuals who do not achieve target levels with high intensity statin therapy and other lipid-lowering agents. Risks, overall for adverse events, were comparable between the PCSK9 and the comparator group, whether that was standard of care,

ezetimibe, etc. We identified two relevant trials that were large enough to assess cardiovascular outcomes, and that was evolucumab in one study and alirocumab in another study. We observed significant reductions that were relative in those studies versus the placebo, but those absolute risk reductions were quite small. So, thanks for listening to me, today talk about PCSK9 inhibitors. I'm happy to take any questions that the committee has today.

Lisa Chew: Thank you, Curtis, for a great presentation. Any questions from the committee members?

Nancy Lee: Thank you, Curtis, for the great presentation. I had a couple questions. It appears that the definition, if you can comment on how the different studies defined intolerance to statins. And then also, in terms of how they defined standard of care would be helpful.

Curtis Harrod: Yeah. So, as you may imagine, the studies had some variation in that. So, the statin intolerance ranged from one trial to multiple trial stem therapies, in which failure to achieve clinical practice guideline thresholds of LDL levels was considered statin intolerant. We do have the full descriptions within the report itself. The second component around standard of care, some was ezetimibe, for instance. Others were statins. And some of those also included physical activity and nutritional guidance and counseling. So, you're really looking at common standard sweeps of treatment for reducing cholesterol levels.

Nancy Lee: Thank you. I had another question about, in your evidence tables where you kind downgraded some of the grades due to, like, a very high risk of bias, can you specify what some of those trends were that you identified?

Curtis Harrod: Absolutely. So, risk of bias was downgraded, in a lot of instances, around conflicts of interest, so manufacturer not only really sponsored the study but they also had some involvement in study design, as well as writing the manuscripts. We have Cochran reviews that demonstrate that is a risk of bias, as studies are more likely to be published if they're positive and sponsored by industry than not. So, we consider that as risk of bias. Other common risk of biases observed within the study, or this topic area, is really small samples. So, you saw a couple that had, like, 64

participants. So, that was another reduction. There was some other biases that we know in the report, but I'll talk about a brief moment here on imprecision. So, that was a main reason our GRADE ratings were downgraded. So, that was just as a result of not many adverse events occurring within the randomized trial, and that creates uncertainty in our findings, as those confidence intervals are quite wide. So, some outcomes are downgraded one level for imprecision, and others were downgraded two levels, as it was very serious imprecision. I apologize. I didn't know in the slide, I was trying to go quickly here today, but key question number five was around subgroup differences. So, I didn't have that in the slide set, because it's kind of underwhelming, honestly, as far as what they've evaluated with regard to harms and benefits of PCSK9 inhibitors. I will note a couple of studies, and this is in the key findings in the report, looked at diabetes status and nondiabetes, or nondiabetics, and they found comparable effects. So, evolucumab had comparable effects to participants on standard of care, whether they had diabetes or not, and then also men and women were compared in subgroup analyses, and they had comparable reductions in LDL levels. So, those are in key findings and just noting that quickly, because that was key question five.

Lisa Chew: Thank you, Curtis. Any other questions from committee members? So, Curtis, there are no further questions. We have one stakeholder, Dr. Sylvia Churchill. Could you please come to the podium? Please state your name, who you represent, and you'll have three minutes.

Sylvia Churchill: Good morning. I am Sylvia Churchill. I am a pharmacist here in Washington State. I work for Amgen as a health outcomes liaison. Really, that review was very thorough, covered pretty much all of the clinical data that we have for the PCSK9's. So, nice job there. The only thing I would do here is just to re-summarize the place and therapy for PCSK9, and it is not meant to be a first in line therapy. Basically, when you have a patient with high cholesterol, you always want to try to start with a statin and give them the maximally tolerated dose that they can take. Where the PCSK9 would fit in is, if a patient is on that maximally tolerated dose of statin, and they still have a significant way to go to get their LDL level down where they want it. So, if you add a PCSK9 on top of the statin, you do see an approximately additional 50% decrease in LDL,

and our outcomes study has shown that that does translate to a decrease in heart attacks and strokes. So, that's where you would want to put it, not firstline but after a patient has already maxed out their statin and needs further reduction in cholesterol. Is there any questions that I can answer for you? Okay. Thank you, very much.

Lisa Chew: Thank you, Dr. Churchill. Okay. So, now we move to the motion. I believe since this is a full report, we don't have to approve the full report. We just, we can look at the prior motion and see if we want to reiterate the prior motion or make edits.

Diane Schwilke: I move that we reiterate the prior motion.

Jordan Storhaug: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. We're going to move on to our next agenda item, which is ADHD. It's a surveillance report, and we have Beth Shaw on the phone and Umang will be after.

Beth Shaw: Good morning. So, if we move on to the next slide. This is the overview of the presentation. So, well take you through the topic history and the background, the method we used in this surveillance report, as well as the findings and the summary.

So, on the next slide, you can see the topic history for this report. It has a long history. So, the update five report was published in July, 2015, and since then, there have been three scans, and this is the one that we conducted in 2019.

On the next slide, you can see the background for this report. So, attention deficit hyperactivity disorder, or ADHD, is one of the most common neurodevelopmental disorders of childhood. It's usually first diagnosed in childhood, but it often lasts into adulthood. We know that children with ADHD have trouble paying attention, they have controlling

impulsive behaviors, or they may be overly active. In 2016, an estimated 6.1 million children aged 2 to 17 years were living in the U.S. with a diagnosis of ADHD. I think there's some really interesting statistics about this. Among those children, 62% were taking medication for their ADHD. So, that's around 1 in 20 of all U.S. children. Again, of those children diagnosed with ADHD, 64% also have another mental, emotional, or behavioral disorder. So, these are children with complex issues.

So, on the next slide, you can see the PICO that we used for this report. In terms of the population, we were looking at both children and adults with ADHD. We were looking at a range of interventions, which we'll see on the next slide. We were looking at head-to-head comparisons. So, we were looking at studies that looked at those interventions compared with each other. Again, we've got a range of outcomes that we'll touch here in the next slide. For this report, we were looking for systematic reviews with or without meta-analysis, as well as randomized controlled trials.

So, moving onto the next slide, we have a long list of included interventions here. From the left hand slide, you can see the generic name. In the middle, we have the brand name. Then, on the right hand side, we have the date of FDA approval. This table is ordered with the most recently approved drugs at the top. We've also categorized them by stimulants and nonstimulants. So, you can see here we've got a range of stimulants, such as amphetamine, methylphenidate hydrochloride, and often we have many different formulations within the same class.

So, moving onto the next slide, again, we continue with those list of stimulants. Then, on the next slide, again, we have the stimulants, but also at the bottom there you can see those three nonstimulants that we were looking for in this report.

On the next slide, we can see the outcomes of interest. So, we were looking for things like symptom response, things like level of inattention, hyperactivity, impulsivity, and a global rating of symptom response. We were looking for functional capacity so that we're thinking about things like social, academic, and occupational activity. We were looking for quality of life, not just of the person with ADHD, but also their family members, their caregivers, and their teachers. Then, we were looking at

other things like time to onset of effectiveness and duration, as well as tolerability and adverse effects. One of the key outcomes that we were looking here, as well, for was misuse or diversion, and that will link into some information that I'll present later.

So, on my next slide, we can see the key questions. We were looking at those comparative efficacy of those pharmacological treatments that we saw, as well as the comparative harm. We were also looking to see whether the effectiveness and harms differed by subgroups. So, we were thinking about demographics, such as age, and also comorbidities. If you [inaudible], nearly 2/3 of children also had a coexisting condition, as well as other medications for those conditions. We were also looking for ongoing studies.

On the next slide, here you can see the methods that we used. So, looking for new randomized controlled trials. We looked at child registry and the FDA website looking for those identified the eligible studies, and then see whether there were any publications. The dates that we searched was from May 2018 to January 2019. We also looked at the FDA website, as well as Centerwatch and Google, for new drugs formulations, indications, or serious harms or warnings.

So, moving into the findings, for the first slide that you can see here, and the next one, is the clinical evidence overview. So, during this surveillance period, we did find one new head-to-head randomized control trial. You can see on the left hand side we have the author, year, and the NCT identifier. Then, we have the population details, active treatment groups, as well as outcome. So, this was a trial that was comparing two different formulations, and that code name is SHP465, extended release. It's the generic name for the longacting drug, Mydayis. So, it's a combination of different drugs for ADHD. In terms of the outcomes, the primary outcome here is the PERMP score. This is an objective validated skill-adjusted math test, but really it measures attention in ADHD. So, higher scores [inaudible] is better, but they also looked at symptom frequency, safety, and tolerability.

On the next slide, we can see three ongoing studies that we identified in the surveillance period. All of them are head-to-head. So, again, you can

see on the left hand side the NCT number moving through the participants, those treatment groups, the outcomes, the true effect in those trials, as well as the enrollment and the primary completion date.

On the next slide, during the surveillance period, there was a new formulation of methylphenidate approved. This is the Jornay drug. This was approved by the FDA in August 2018, and it's actually a combination of an extended and delayed release capsule, and it was approved for ADHD in patients age 6 and older. The reason that it was this combination of formulation was it's intended to be taken in the evening with the timing adjusted to optimize the tolerability and efficacy the next morning and throughout the day. In terms of the effectiveness of Jornay P.M., this is established in two separate phase [inaudible] center randomized with a blind placebo controlled study, and they were conducted in a total of 278 children aged 6 to 12 years with ADHD.

So, moving onto the next slide, in terms of new serious harms or warnings, well, for years, these CNS stimulants, such as methylphenidate and amphetamine, they have a black box warning related to the high potential for abuse and dependence, hence why we were looking for that outcome of misuse or diversion. So, this serious harm or warning has been known for many years, but since 2019, some of the prescribing labels for the drugs for ADHD were updated to include this safety warning that had already been know, and this black box warning also applies to that newly improved formulation, Jornay P.M.

Next slide, please. So, looking at the summary, in terms of the new clinical evidence, you can see here we have eight head-to-head randomized control trials, since the update report, one of which was identified during this surveillance period. We have seven secondary analyses, since the update report. Again, none during this surveillance, and we identified three ongoing head-to-head studies, which you saw the details of.

On the next slide, you can see the FDA actions. So, we didn't find any new drugs, but there have been nine new formulations in this particular area, and one during that surveillance period, the Jornay P.M.

On the final slide, you can see no new indications, but again, just that known safety warning that has been added to more product labels during this surveillance period. Thank you.

Lisa Chew: Any questions from the committee members? Okay. Beth, there are no questions, so Umang, do you want to present?

Umang Patel: Okay. So, just a reminder to the committee members, usually how the presentations are, there will be a little bit of an overview, indications, dosage and formulations, and guideline reviews, as well. There are a number of different topics today that do have new drugs that weren't updated in the TCRs, the therapeutic class reviews that I will be presenting separately, as well.

So, on the next slide here, just to give a little background for ADHD, attention deficit hyperactivity disorder, it's been diagnosed in approximately 15% of children 4 to 17 years of age, and about 4% of adults. It is a chronic condition with core symptoms of inattention, hyperactivity, and difficulty controlling behavior. It may also be accompanied by internalized disorder, such as sadness and anxiety, as well as aggressive and oppositional disorders. There are three main subtypes of ADHD, primary hyperactive, primary inattentive, and mixed. Children with ADHD may experience academic underachievement, difficulties in personal relationships, low self-esteem. Symptoms tend to improve with age; however, this may be due, in part, to improved coping skills. The continuation of synaptogenesis and myelination into adolescence and young adulthood, especially in the frontal lobes, may also play a role in the improvement of symptoms. One-third of children with ADHD will retain the diagnosis, as they enter into adulthood.

On the next slide here, we have hypersomnolence, excessive sleepiness or hypersomnolence is the primary and often debilitating symptom experienced by patients with narcolepsy, obstructive sleep apnea, hypopnea syndrome or OSAHS, and shift-work sleep disorder, SWSD. The defining characteristics of hypersomnolence is a consistent inability to stay awake and alert enough to safely and successfully accomplish tasks of daily living. Persons experiencing excessive sleepiness who seek medical attention typically contain of fatigue, tiredness, lapse of

attention, lack of energy, low motivation, difficulty concentrating, disrupted sleep, snoring, or difficulty at work. In terms of treatment, while CPAP therapy has been shown to improve daytime sleepiness in patients with OSA, the level of sleepiness does not always normalize. To address this residual daytime sleepiness, pharmacological treatments may be beneficial in users of CPAP. Medications such as Provigil, Nuvigil, and Sunosi are FDA approved for excessive daytime sleepiness associated with OSAHS. Again, Provigil and Nuvigil are also indicated for sleep problems resulting from circadian rhythm disruption, such as shift work sleep disorder. Provigil, Nuvigil, and Sunosi, along with central nervous system stimulants, such as dextroamphetamine, Procentra, methylphenidate, mixed amphetamine salts, and amphetamine sulphate tablets, are used for narcolepsy. The potential for adverse cardiovascular events with CNS stimulant, use may be of concern, especially in this overall high-risk patient population. Due to their lack of sympathomimetic activity, Provigil and Nuvigil are relatively free of adverse cardiovascular risks.

To pivot over to the guidelines for ADHD, according to the American Academy of Pediatrics in 2011, the primary care clinician should initiate an evaluation of ADHD for any child 4 to 18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, and impulsivity. The treatment of patients with ADHD should maximize function to improve relationships and performance at school, decrease disruptive behaviors, promote safety, increase independence, and improve self-esteem. In terms of treatment, it recommends parents and/or teachers administer behavior therapy, as firstline for children 4 to 5 years of age. Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement, and there continues to be moderate to severe disturbance in the child's function. For children 6 to 11 years of age, the evidence is particularly strong for stimulant medication use and sufficient, but less strong evidence for atomoxetine, extended –release Guanfacine, and extended-release clonidine; however, medication therapy in addition to behavioral therapy is recommended. Lastly, for patients 12 to 18 years of age, the guidelines recommend FDA approved medications with the adolescent's assent and behavior therapy as treatment for ADHD, preferably both.

Last slide for guidelines, according to the Medical Letter in 2011, they suggest that school-aged children begin with oral stimulants noting that none of the agents have been shown to be more effective than another. They indicate short-acting stimulants may be useful in small children to demonstrate effectiveness or in instances where there is not an appropriately low dose of longacting agent. The methylphenidate patch, Daytrana, is recommended for use when oral administration is problematic. Strattera, a nonstimulant agent, is recommended if there are objections to using a controlled substance, if stimulant induced weight loss is problematic, or for patients with anxiety, moods, tic, or substance use disorders. Extended release formulations of Guanfacine or clonidine may be helpful when used concurrently with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Lastly, mixing short and longacting stimulants can be helpful to achieve an early stimulant effect for early morning school classes, or for reducing rebound irritability or overactivity toward the end of the day, especially when studying in the evening. Just to note, the AACAP, the American Academy of Child and Adolescent Psychiatry practice parameters for ADHD are now categorized as historical and can no longer be assumed to reflect current knowledge, as they have not been updated in over five years, but they are currently in... a newer version is in development right now.

So, on the next slide here, over the next few slides, we'll have the indications and then the dosing and availability for stimulants. Then, I've stratified it for stimulants and nonstimulants. So, here you have the indications for stimulants. Again, we have Evekeo, Evekeo ODT, Nuvigil, Focalin, Zenzedi, Procentra, Desoxyn, and Methylin or Ritalin here, along with their respective, whether they are available in generic, their respective indications that are sub-stratified by age for ADHD, if it is approved for narcolepsy, and for completeness sake, any other indication that they may provide, such as exogenous obesity, OSA or SWD, and etc. While I give you a second here, I know historically some of the committee members have appreciated the pharmacology behind them. So, just to give you a little bit of background, in terms of the MOA, the stimulants act by blocking up the reuptake of the norepinephrine and dopamine in the presynaptic neuron and increase the release into the extra neuronal

space. Amphetamines appear to release newly synthesized dopamine while methylphenidate causes the release of stored dopamine. Unlike methamphetamine, the amphetamine induced elevation of synaptic dopamine does not appear to be highly dependent upon impulse released dopamine. Stimulants tend to have selectivity for cortical rather than striatal dopamine presynaptic terminals. As a result, lower doses have more of an effect on attention than on motor activity. Lastly, symptoms of inattention in ADHD may be due to dopamine and/or norepinephrine dysfunction in critical areas of the cerebral cortex. It appears that patients with inattention symptoms need a boost in their dopamine and norepinephrine. When they are given agents, such as stimulants, to boost these symptoms, their symptoms of inattentiveness can improve.

Moving onto the next slide here, we have stimulants for immediate release continued with Adderall and Provigil. Then, it pivots over to the extended release stimulants. We have Adzenys ER, Dyanavel XR, Focalin XR, Dexedrine, Vyvanse, and methylphenidate ER. I'll give you a second or two just to kind of absorb this, and we'll continue onto the last slide for indications for stimulants.

Okay. And on the last slide here for the stimulants, we have extended release continuing with Adhansia XR, Aptensio XR, Cotempla XR-ODT, Jornay P.M., Metadate ER and Ritalin SR, Quillichew ER and XR, Ritalin LA, Concerta, Daytrana, Adderall XR, and Mydayis. So, just to note, stimulant agents, such as amphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate, methaphenidate, and mixed amphetamine salts are all schedule 2 controlled substances. Armodafinil, modafinil, and Sunosi are schedule 4 substances, which I'll cover in the next few slides. Please note that there are contraindications. All products in this review, except for clonodine ER, Guanfacine ER, and modafinil, excuse me, armodafinil and modafinil, are contraindicated during or within 14 days following the use of an MOAI, monoamine oxidase inhibitor, and concurrent use can prolong and intensity the cardiac stimulation and vasopressor effects of stimulants. There is black box warning, such as my colleague before me pointed out. Stimulants have warnings, many with boxed warnings regarding the high potential of abuse. Prolonged use of these agents can lead to drug

dependence, tolerance, and social disability. Prescribers should assess the risk of abuse prior to prescribing, monitor patients for signs of abuse and dependence, and reevaluate the need for stimulants. Stimulants should be used with caution in patients with preexisting psychosis, bipolar disorder, or aggression, as these conditions can be exacerbated. Treatment, emergent, psychotic, or manic symptoms have been reported in 0.1% of patients receiving stimulants, and 0.2% of patients receiving Strattera. I apologize. There's a few more slides for the stimulants. We have immediate release here. Now, for this, for the dosing and availability, I'm not gonna go through each of the dosing. This is more, again, for the committee's completeness sake, but just to give you a few... a little bit of background on some of these, again, as my colleague mentioned, there is a cardiovascular risk with some of these medications. Sudden death, stroke, and MI's have been reported in adults using stimulants at recommended dosages. I has also been reported in association with stimulants and atomoxetine at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Stimulants and atomoxetine generally should not be used in patients with known serious structural cardiac abnormalities, cardiomyopathy, heart rhythm abnormalities, or other serious cardiac problems. In terms of growth, the 2011 AAP clinical practice guidelines acknowledges that appetite suppression and weight loss are common adverse effects of stimulants, but studies of stimulants use have found little or no decrease in expected height. Any decrease in growth early in treatment is later compensated.

Onto the next slide here, we have more dosing and availability. While this is in front of you, to give you information about special populations in terms of patients who are pregnant, Guanfacine ER is pregnancy category B, as in Beta. Mydayis essentially majority of them have not been assigned a pregnancy category based on FDA's revised pregnancy risk formatting. Nuvigil is pregnancy category C. Armodafinil should only be used during pregnancy if the potential benefits justify the potential risk. In terms of renal and hepatic dosing, dose reductions of Strattera are required for patients with moderate and severe hepatic impairment. The dose of Nuvigil should be reduced in patients with severe hepatic impairment, and patients 13 to 17 years of age with severe renal impairment may receive the recommended starting dose if tolerated;

however, the dose should not be increased. In terms of mixed amphetamine salts, Adderall XR, Mydayis, it is not recommended for use in patients with endstage renal disease, and a lot more dose adjustment can be found in the therapeutic class review, as well.

For the last slide of the stimulants here, again, just for completeness sake, and then to pivot over to the nonstimulants. So, here we have Strattera, Kapvay, Intuniv, and Sunosi. To give mechanism of action on these, Strattera is a selective inhibitor of presynaptic norepinephrine transporter. It increases norepinephrine and dopamine levels, especially in the prefrontal cortex. Intuniv is a selective Alpha-2A adrenergic receptor agonist. Kapvay is essentially acting Alpha-2 adrenergic receptor agonist. These drugs reduce sympathetic nerve impulses to the heart and blood vessels, leading to a decrease in blood pressure. Sunosi is a dopamine norepinephrine reuptake inhibitor. Its mechanism to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy or OSA is unclear.

On the next slide here, there is a medication that was recently approved in August 2019. So, the reason this is being specifically reviewed is because our therapeutic class reviews are periodically reviewed. This medication was just approved roughly two months ago. So, it is not in the TCR, but I did want to give background information on it. Medication is named Wakix, or pitolisant. An NDU is in the web portal for the committee. It is a histamine-3 receptor antagonist inverse agonist, and it is indicated for the treatment of excessive daytime sleepiness in adult patients with narcolepsy. Now, it is contraindicated in patients with severe hepatic impairment. It does prolong the QT interval with a corrected QTC increase of 4.2 milliseconds at the highest recommended dose. So, its use should be avoided in patients with known QT prolongation or those using other medications that prolong the QT interval. Wakix should be avoided in patients with a history of cardiac arrhythmia, similar to others in this class, or those at risk for torsade or sudden death. Hepatic or renal impairment may increase the risk of QT prolongation due to increase in serum concentration. The dosage is here listed for you. The achievement of clinical response may take up to eight weeks. So, please keep that in mind. And the availability is in tablet

forms, although the dose at 5 mg and 20 mg, which are equivalent to the 4.45 mg and 17.8 mg free base respectively.

Its place in therapy, again, a lot of these guidelines are somewhat outdated, according to the American Academy of Sleep Medicine. CNS stimulants are the standard of care for EDS. Modafinil or armodafinil is preferred as the standard initial treatment, due to the more favorable side effect profile and less addictive properties when compared to older stimulants. Second line treatments, include methylphenidate and amphetamine stimulants. Historically, these medications have been the most widely used in clinical practice, but clinical evidence remains limited. Wakix offers an additional treatment option for the treatment of EDS with a novel mechanism of action. Furthermore, it lacks a controlled substance designation; however, it requires a dose adjustment in special populations, such as hepatic and renal impairment and drug interactions, as well as the established role of stimulants for the treatment of EDS may limit its use.

Lisa Chew: Thank you, Umang. Any questions from the committee members? Okay. We have one stakeholder here, Dr. Deb Profant. Please come to the podium. Please state your name and who you represent, and you will have three minutes. There are also two documents in your binder from other stakeholders, as well.

Deb Profant: Okay. My name is Deborah Profant. I am one of the managed care liaisons from Jazz Pharmaceuticals. We are the manufacturer of Sunosi. So, I'm gonna just give you a brief update about Sunosi or solriamfetol. Sunosi was approved in March 2019 for the indication of excessive daytime sleepiness in patients with narcolepsy and obstructive sleep apnea. Sunosi has a schedule 4 designation, and Sunosi is not indicated to treat the underlying airway obstruction in OSA. So, the limitation of the use is that it's recommended that patients continue some form of primary airway therapy. We did enroll in the trials patients who were compliant with their primary airway therapy but also patients who were noncompliant based on discussion with FDA. So, solriamfetol is a dopamine norepinephrine reuptake inhibitor, and FDA approval was based on the phase 3 clinical program for adult patients with narcolepsy and a separate study of adult patients with OSA. The magnitude of

solriamfetol's effects are clinically meaningful. At week 12, the wake-promoting effects of the 150 mg dose, which is the highest dose approved, was evident one hour after dosing and persisted through each of the five 40-minute trials during the day, which is nine hours after dose. A high percentage of patients with OSA, up to 73%, and narcolepsy population up to 49% achieved a normal score on the Epworth sleepiness scale. So, we did both subjective measures of sleepiness and objective measures, as monitored by a sleep technician. Importantly, there were no clinically meaningful differences in efficacy across all subpopulations that were defined. So, efficacy was not different based on age, gender, or race, or BMI, the presence of cataplexy for the narcolepsy patients, baseline use of primary OSA therapy, or baseline severity of sleepiness. No studies were performed with an active comparator. There are no existing head-to-head studies. Instead, we did an indirect treatment comparison using a meta-analysis of available clinical studies. In that meta-, in that indirect treatment comparison, solriamfetol demonstrated significant improvement in wakefulness compared to both modafinil and armodafinil at the highest doses. Across all the solriamfetol studies, the most common AE's are headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth. Discontinuation rates were low across the studies at 3%. I'll take any questions if there are any.

Lisa Chew: Any questions? Alright. Thank you, very much. Okay, let's look to the motion. So, since this is a surveillance report, new drugs cannot be added to the PDL here. Do we, is it a similar process to a scan? We have to approve the surveillance report as adequate or not adequate, that you want a more thorough review. Right? Similar to a scan.

Nancy Lee: I propose that the surveillance report is adequate for ADHD medications. I don't know the exact wording.

Virginia Buccola: I would second that motion.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. Then, I think we need to move to the motion, the prior motion is listed here from June 20, 2018. It looks like it's three sections, one about the methylphenidate based and amphetamine based agents. The second one is the nonstimulant atomoxetine. Then, the third one is the alpha-agonists.

Virginia Buccola: I would propose that we reiterate the prior scan as adequate. Is that correct wording, prior motion. Thank you.

Susan Flatebo: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. It looks like we have a ten-minute break. So, I can't add, 10:20. Okay.

I think Shannon and then Umang will be presenting.

Shannon Robalino: Hi. This is Shannon Robalino, a research associate with DERP. I'll walk you through the surveillance documents on biologic drugs to treat asthma and chronic spontaneous urticaria. If you clip to the first slide, I'll provide you a quick overview of what this presentation is. It's similar to the last one that you heard with some topic history and background, the methods, and then the findings and conclusions.

Just a brief bit of topic history. There was a systematic review published in April of 2018 that included 13 RCT's, 4 systematic reviews, and 2 observational studies for asthma. For chronic spontaneous urticaria, I'll refer to it as CSU from now on. There were two RCT's and one systematic review. There were no head-to-head studies in this review.

Just a brief bit of background. There are currently five drugs approved by the FDA. The oldest was approved in 2003, omalizumab. And the most recent was approved in October of 2018. This is dupilumab, which was originally approved in 2017 for atopic dermatitis, but approved in 2018 for asthma. Only one of these five drugs is approved for asthma and CSU.

This table, you'll see the five drugs, the generic name, the brand name, the indication, and the date of FDA approval. The drugs target specific interleukin receptors. The newest drug, dupilumab, targets interleukin receptor 5 and the remainder of them target interleukin receptor 4.

The PICO for this surveillance document, we were interested in adults or children with persistent or chronic asthma and adults with CSU. Interventions of interest were of the five FDA-approved drugs. The comparators of interest are placebo or usual care, including add-on studies, or any of the five drugs compared to each other. Outcomes of interest for asthma included severe exacerbations requiring emergency care or hospital admission, symptom control, quality of life, or mortality. For CSU, outcomes of interest included urticaria activity scores of less than or equal to 6, symptom control, such as itching, quality of life, use of other medications for urticaria, but the surveillance document we were only interested in RCT's.

We had three key questions. The first two are around the effectiveness and harms of these biologic medications for the two conditions, asthma or CSU. And the third question is around ongoing studies for these medications in asthma and CSU.

Our methods, as previously discussed, we searched for clinical trials in clinical trial registries, such as clinicaltrials.gov, and an international trials registry. Using the trial numbers identified there, we then searched in OVID Medline for systematic reviews and interventional studies. We didn't include any systematic reviews in this, but we did check them for potential studies of interest. We also searched websites for FDA actions, including the FDA and a general internet search. The searches for this document covered October 2017 through August 20, 2019.

We'll start to go through the findings. For this document, there was one new drug, a formulation identified. The new drug for this topic, again, was dupilumab, initially approved by the FDA in 2017 for atopic dermatitis. It was approved for asthma in October of 2018, as an add-on treatment for moderate to severe asthma in patients aged 12 or older.

New drugs of formulation, there were two new formulations identified, mepolizumab for asthma is available as a prefilled auto injector or prefilled syringe, and omalizumab for CSU. There is now a prefilled syringe available.

Now moving to the findings of new studies. These are RCT's. This is just a summary slide, and I'll walk you through these in a little bit of detail. There were 13 new studies identified for asthma. No new head-to-head studies, and no new studies for CSU. I'll walk through these briefly in reverse chronological order with the newest drug first.

For dupilumab, we identified three RCT's. These were generally larger trials with study durations of six months to one year comparing different dosages of dupilumab to placebo in patients with asthma.

For benralizumab, we identified four RCT's. All four tested benralizumab 30 mg to placebo. The RCT's had a duration of three months to just over three years. Just to note that the two trials in the middle, Goldman and Nair focus on populations with specific blood eosinophil counts.

For reslizumab, we identified one open-label extension study. The participants had blood eosinophil counts above 400 cells per microliter. And participants received treatment for up to 2.2 years.

For mepolizumab, we identified two RCT's. They were poor on different subgroups. You can see the first one reports on a subgroup with severe eosinophilic asthma, and the second in Japanese patients. These trials had durations of six to eight months.

We also identified two patient-level meta-analyses. These both came from multiple trials in patients with blood eosinophil levels at different thresholds and compared mepolizumab to placebo. Again, these had trial durations ranging from six to eight months.

For omalizumab, this was the last of the new studies that we identified. This compared omalizumab by weight to placebo in patients already on a stable dose of the drug for at least two months prior to the start of the study. The participants were treated for up to one year.

We now move on to the next slide. These are going to be ongoing trials that were again applied in the trials registry but have not had any published evidence.

Again, just an overview slide. The first will be ongoing studies for asthma. There were 19 potentially relevant ongoing studies.

This was the only head-to-head study that we identified comparing mepolizumab to omalizumab, and it is due to complete in December of 2020.

For dupilumab, we identified eight ongoing studies, five of these are RCT's, and three are open label extensions. The study sizes range from 32 to just over 2000. The two studies in bold on this table are in pediatric populations, aged 6 to 12.

For benralizumab, we identified four ongoing studies. Three of these are RCT's, and one is an open label extension. Again, larger trial sizes, one that recently completed in August of 2018 but has not published anything as of yet.

For reslizumab, we identified one ongoing RCT. It completed in January of 2018 and has posted some results on clinicaltrials.gov, but as of August 2019, there were no peer-reviewed publications.

For mepolizumab, we identified three ongoing RCT's. Again, the study in bold is the one in the middle. It is in the pediatric population, age 6 to 17. That completed in September of 2019.

For omalizumab, we identified two RCT's, one was a smaller study. Again, the study in bold is in a pediatric population [inaudible] on this slide. It is in children ages 2 to 4.

I'll walk you through the ongoing studies for CSU. Again, just a summary slide of the studies identified. There were four ongoing studies identified, and just to note that the two drugs, dupilumab and

benralizumab, are currently not approved by the FDA for treatment in this population.

For dupilumab, one small RCT in patients with CSU. Again, this is not currently an approved treatment in this population.

For benralizumab, another small study for patients with CSU. Again, not approved by the FDA.

Omalizumab is the only drug that is approved by the FDA. You can see that we identified two ongoing RCT's. They're both larger RCT's. The second RCT on this slide is actually comparing omalizumab to a pipeline drug.

Just to give you a summary of what I've just talked through, since the completion of the systematic review in April 2018, there was one new drug for the treatment of asthma. This was dupilumab for add-on treatment in moderate to severe asthma. Just a reminder that this was originally approved in 2017 for atopic dermatitis, but approved for asthma in 2018. Two new formulations, mepolizumab as prefilled auto-injector in a prefilled syringe, and omalizumab as a prefilled syringe.

On this final slide, just the clinical evidence. We identified 13 RCT's, published RCT's, all in asthma. None of these were head-to-head studies. Ten are placebo-controlled trials, one an open label extension, and two patient-level meta-analyses of large RCT's. There were 23 ongoing studies, 19 in asthma and 4 in CSU. Only one of these is a head-to-head study, 18 are placebo-controlled trials, and four are open-label extensions. We did not identify any new indications, serious harms, or warnings. Now I'll take any questions. Thank you.

Lisa Chew: Thank you, Shannon. Any questions from the committee members? Okay. There are no questions.

Umang Patel: Okay. So, next, we'll cover antiasthmatics, monoclonal antibodies covering both IL-5 antagonist and IGE antibodies. A little overview of the disease state, so prevalence of asthma in the United States continues to rise. An estimated 7.7% of adults and 8.4% of children, which is roughly

25 million Americans, have asthma with approximately 10 to 20% in poor control. The NAEPP, or the National Asthma Education and Prevention Program, has defined asthma as a chronic inflammatory disorder of the airways, in which many cells and cellular elements play a role. Asthma phenotypes have been identified by clinical and/or pathophysiological characteristics. It has been established that eosinophils play a role in the inflammatory process of asthma, and eosinophilic asthma is identified as a phenotype of asthma. Generally, patients with eosinophilic asthma have severe disease with high eosinophil levels in the blood and sputum despite treatment with the glucocorticoid. Persistent levels of these eosinophils in sputum may also be an indicator of disease severity.

Here, we'll take a step to urticaria. The reason is, some of these medications I will be going over have additional indications. So, this is just, again, for completeness sake. So, the prevalence of chronic urticaria, or CU, is estimated to be 0.5 to 5% of the general population. It presents as pruritic edematous red wheels of variable size and shapes with surrounding erythema. It's defined as episodic or daily hives lasting for six weeks or more that impair quality of life. The major cases have an undetermined cause; however, infection and autoimmune conditions can be associated with CU. It also may be associated with the presence of mononuclear cells, eosinophils, neutrophils, basophils, MAST cells, and activated macrophages.

Lastly, eosinophilic granulomatosis with polyangiitis previously known as Churg-Strauss syndrome, is a system vasculitis of small to medium vessels characterized by allergic rhinitis asthma, and hypereosinophilia. It's a rare disease effecting one to three out of 100,000 patients with higher incidence of 1 per 15,000 with asthma. Onset occurs between 15 and 70 years of age, but diagnosis is typically made between 35 and 50. While the direct cause of this is unknown, HLA-DRB4 positivity maybe a genetic risk factor. Symptoms can vary from mild to life-threatening. In terms of diagnosis, a diagnosis may be confirmed if in addition to vasculitis, patients also have at least four of the following features, asthma, eosinophilia, neuropathy, pulmonary infiltrates, paranasal sinus abnormalities, and eosinophilic vasculitis. Scoring systems to assess the severity of vasculitis and guide initial therapy in patients with EGPA include the five factor FFS and the Birmingham vasculitis activity score,

BVAS. Additional details below. In terms of guidelines, there are no US guidelines currently available for the treatment. As a consensus, it is not severe in nature and is often treated with corticosteroids, oral corticosteroids, and more than 90% of patients achieve remission. Initial therapy may also include cyclophosphamide for patients with severe multiorgan disease. Patients with severe EGPA may be transitioned to maintenance therapy with azathioprine, methotrexate, or leflunomide. Evidence supporting their use is limited. Other treatments include anti-IL-5 antibody, such as Nucala, immunoglobulins, interferon-alpha, rituximab, and inhaled glucocorticoids may be used. Notably, Nucala is the only FDA approved medication for this disease state.

So, to pivot over to the indications, in this class, we have, again, IL-5 antagonists, which are comprised of Fasenra, Nucala, and Cinqair. All are indicated for the add-on maintenance treatment of patients with severe asthma age greater than or equal to 12 years of age and with an eosinophilic phenotype. Nucala has an additional indication of the treatment of adult patients, again, with EGPA, as mentioned previously. Cinqair is the only difference is, it is 18 years of age or older. For IGE antibodies, we have Xolair, which is indicated for moderate to severe persistent asthma in patients 6 years of age or older with a positive skin test, or in vitro reactivity to perennial aero allergens and symptoms that are inadequately controlled with inhaled corticosteroids. It is also indicated for CU in adults and adolescents 12 years of age or older who remain symptomatic despite H1 antihistamine treatment. Please note that Dupixent is also a medication that is in this class; however, it's also in a class we'll be covering right after this. So, in order to prevent duplication, I'll be covering it more in depth in that class, but Dupixent, or dupilumab, is an interleukin-4 receptor alpha-antagonist. It's not included, again, in this TCR. It is indicated as an add-on maintenance treatment in patients greater than or 12 years of age with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

We have dosing and availability. The dosages, administration, comments, and dosage forms are here in front of you. Please note, Fasenra, Nucala, and Xolair are administered subcutaneously where Cinqair is IV only. Fasenra, Cinqair, and Xolair are indicate to be administered by a

healthcare professional. Patients or caregivers can administer Nucala using the prefilled auto-injector or prefilled syringe following proper training, if a healthcare practitioner determines it to be acceptable. The vial of preparation for Nucala requires reconstitution and administration by a healthcare professional. In terms of this class, there is a blackbox warning, uh, for Xolair and Cinqair, it carries a black box warning of anaphylaxis. Xolair has been reported to occur after the first dose and up to one year after the beginning of the treatment. Time onset reported is roughly 90 to 120 minutes after administration. For Cinqair, anaphylaxis is also reported roughly 20 minutes after infusion. Although labels for Fasenra and Nucala do not contain blackbox warning, hypersensitivity reaction can occur within hours to days of dosage being given. Please note, none of these agents should be used to treat acute asthma symptoms, or asthma exacerbations.

The ATS, or the American Thoracic Society, and the European Respiratory Society Task Force in 2014, defined severe asthma as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled where that remains uncontrolled despite therapy. The guidelines suggest a trial of Xolair in adults and children aged 6 years and older with a confirmed IGE dependent allergic asthma, despite optimal drug and nondrug therapy. If there is no response within four months of beginning Xolair, it is unlikely that continued treatment will benefit. Fasenra, Nucala, and Cinqair were not available at the time these guidelines were published. So, please keep that in mind.

Moving over to the GINA guidelines, the Global Initiative of Asthma Guidelines, these guidelines are going to be popping up today, I believe in about two other classes. So, for completeness sake, I'll go over it this time, but moving forward, I may just brush through it quickly. The guidelines offer a management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response, as it relates to symptom control, future risk of exacerbations, and side effects. During this continuous cycle, a stepwise treatment approach is used to achieve control using the patient's current level of control, as the baseline. If the patient is not controlled on the current regimen, treatment should be stepped up until control is achieved. According to

the stepwise approach, patients in steps one and two are considered to have mild asthma. Patients in three to four are moderate. Patients in steps four to five are moderate to severe. The guidelines recommend that all adults and adolescents with asthma receive an inhaled corticosteroid containing controller medication. Due to the increased risk of severe exacerbation in asthma-related death, SABA's, or short-acting beta agonists only treatment is no longer recommended. For most asthma patients, treatment can be initiated with an as-needed low-dose inhaled corticosteroid formoterol step 1, or daily low-dose inhaled corticosteroid step 2. In patients whose asthma is uncontrolled on a low dose inhaled corticosteroid containing controller, despite good adherence and correct technique, a step up in treatment may be added. The tables on the next slide will help delineate this. Any step up therapy should be reassessed after two to three months. If there is not an adequate response, consider alternative treatment options or a referral, and if asthma control is maintained for at least three months on the current regimen, treatment can be stepped down to the lowest step, and dosage that maintains controls.

The next slide will have the tables, but to continue with the GINA guidelines, severe asthma is uncontrolled asthma despite adherence with optimized step 4 or 5 treatment, correct inhaler technique, and proper management of contributory factors, where asthma that worsens when high dose therapy is decreased. If asthma is uncontrolled after three to six months on high-dose inhaled corticosteroids and a LABA combo, it is recommended to refer to a specialist and phenotype into categories, such as severe allergic aspirin exacerbated, or eosinophilic asthma, as this may guide the selection of an add-on treatment. For add-on treatments for severe asthma, including Spiriva or low-dose azithromycin, which is off-label, a leukotriene receptor antagonist, monoclonal antibody, such as Fasenra, Nucala, Xolair, or Dupixent, a low-dose oral corticosteroid, or bronchial thermoplasty or sputum-guided therapy could be considered. Patients with severe allergic asthma with elevated IGE levels may benefit from Xolair therapy with a GRADE of evidence A. Those with eosinophilic asthma may benefit from Fasenra, Nucala, and Cinqair anti-IL-5 therapy, evidence A. Those with severe eosinophilic type 2 asthma, or patients requiring maintenance oral corticosteroids may benefit from Dupixent,

evidence A. Those with aspirin sensitivity may benefit from leukotriene receptor antagonist, evidence B.

So, everything I said here just is delineated in this table on the next slide here. As you can see, the GINA guidelines are broken down between all these steps, 1, 2, 3, 4, and 5. That's further broken down by age group, and then preferred controller and other controller options, as well. Everything I just said is listed here. So, I won't go through it again.

On the next slide here, you see step 4 and step 5, and the definition of those are below. Then, on the next slide here, you have the GINA guidelines for reliever therapy.

Okay. On the next slide, for urticaria, the American Academy of Allergy Asthma and Immunology, or AAAAI, the American College of Allergy Asthma and Immunology, the ACAAI, and the Joint Council of Allergy Asthma and Immunology, the JCAAI, recommended stepwise care approach for chronic urticaria. These guidelines were in 2014. Treatment should begin based on patient's level of severity and previous treatment history. At each level, medication should be evaluated for efficacy and patient tolerance, and stepdown should be considered when consistent control is received. For step 1, monotherapy with second generation antihistamines is considered firstline for CU, in addition to avoid of trigger, such as NSAIDs, food allergens, and relevant physical factors. If that is not sufficient, then step 2 where CU is not controlled, the antihistamine dose can be increased, if appropriate for that particular agent. One of the following can be added, another second generation or first generation antihistamine, H2 antagonist or a leukotriene receptor antagonist. If control is still not received, then in step 3, dose advancement of a potential antihistamine, such as hydroxyzine or doxepin, may be considered as tolerated. If that still does not achieve control or CU that is refractory to maximal antihistamine therapy in step 3, alternative agents, such as Xolair can be used. Other anti-inflammatory immunosuppressants or biologic agents may be considered, but have a lower level of supporting evidence.

Lisa Chew: Umang, thank you very much. Any questions for Umang? Okay. We have two stakeholders, Dr. Meredith Zarling and Dr. Thomas Plucinak.

Please come to the podium, state your name, who you represent, and you will have three minutes.

Meredith Zarling: Hello. My name is Meredith Zarling, and I am a pharmacist in Washington, as well as the medical science liaison at Sanofi Genzyme. Today, I'm going to review clinical highlights of asthma indication for Dupixent. As you just heard, Dupixent is an interleukin-4 receptor alpha-antagonist, which is indicated for add-on maintenance treatment in patients with moderate to severe asthma aged 12 years of older with an eosinophilic phenotype or for patients who have critically steroid dependent asthma. The approval of Dupixent for moderate to severe asthma was based primarily on three randomized double-blind placebo-controlled trials with a total of 2888 subjects, aged 12 years of age and older. Trials 1 and 2 had co-primary endpoints of severe asthma exacerbations and lung function. In an attempt to treatment patient population, and again the patients were enrolled without a minimum biomarker requirement. Subjects receiving Dupixent had significant reductions in the rate of asthma exacerbations compared to placebo. Additionally, subjects receiving Dupixent had reduced rates of hospitalizations and Emergency Room visits due to exacerbations compared to placebo. In regards to lung function, which is measured by a pre-bronchodilator FEV-1, significant increases were observed at week 12 in the primary analysis population compared to placebo. Study 3 evaluated the effect of Dupixent in reducing the use of oral maintenance corticosteroids with the primary endpoint being the percent reduction from baseline in the final oral corticosteroid dose at week 24 while still maintaining asthma control. Compared to the placebo, subjects receiving Dupixent achieved greater reductions in daily maintenance, oral corticosteroid dose while still maintaining asthma control. The mean percent reduction in daily OCS [inaudible] for oral corticosteroid dose from baseline was 70% subjects receiving Dupixent compared to 42% in subjects receiving placebo. Reduction in the 100% of the oral corticosteroid dose was present in 52% of subjects receiving Dupixent versus 29% in the placebo group. So, to summarize, Dupixent was superior to standard care, which was medium to high dose inhaled corticosteroid plus a required second controller for both co-primary endpoints, reductions in severe exacerbations, and improvement of FEV-1. There was no benefit in patients with baseline blood eosinophils less

than 150 compared to placebo. Dupixent significantly reduced oral corticosteroid use while simultaneously reducing severe asthma exacerbations and improving FEV-1 in patients with oral corticosteroid dependence, severe asthma. Most common side effects include injection site reactions and eosinophilia. Thanks for your consideration. I am happy to answer any questions you might have.

Lisa Chew: Thank you, Dr. Zarling. Any questions? Okay. Thank you.

Thomas Plucinak: Alright. So, good morning, everybody. I'm Tom Plucinak. I am a Ph.D. biochemist by training. I'm the GlaxoSmithKline respiratory medical science liaison for the Pacific Northwest. In this role, I provide clinical support for all our asthma and COPD medications. So, there are three main points relative to mepolizumab I'd like the group to consider. Number one is going to be that mepolizumab now has a pediatric severe asthma indication, which due to a timing issue was not reflected in the surveillance report that was very nicely presented earlier. Number two, an important point, is mepolizumab now has open-label extension safety and efficacy data in severe asthma out to four and a half years in some patients, which is no small feat. Among its category, number three, mepolizumab has a unique range of indications and formulations. So, now, I'll just say a little bit more detail on each one of those topics. So, number one, about the pediatric indication, as of September 12th, 2019, Nucala was approved by the FDA for the treatment of severe asthma down to the age of 6. This is especially impactful to this group, because many children with severe asthma tend to be inner city Medicaid patients and account for a significant portion of healthcare resource utilization and hospitalizations among the pediatric asthma population. Longterm safety, as of now GSK has now conducted three open-label extension studies with mepolizumab in 900+ patients with severe asthma. The efficacy and safety profiles closely match findings from our phase 3 studies. No new safety issues were identified, and efficacy remained remarkably consistent. As mentioned before, also of note here is that some patients were enrolled up to four and a half years, which means in combination with phase-3 data, we have about five and a half years of data in some patients. So, a unique range of indications. In addition to its severe asthma indication, mepolizumab is the only biologic of any type of proof for the treatment of EGPA. It is the only IL-5 agent approved for

pediatric severe asthma. Additionally, as of June 2019, a new at-home self-administration formulation became available, which was covered nicely, as well. This means that HCP's and patients now have the option to administer or receive this medication in a clinic or at home. Because many patients and HCPs have strong preferences and requirements for in-office or at-home administration, we feel this greater versatility will be of benefit overall. So, to summarize, accordingly, due to mepolizumab's unique combinations of indications among this category, the severe asthma for adults and pediatrics, EGPA, enhanced versatility of the in-office, as well as at-home formulations, for self-administered formulations, in addition to our established longterm safety and efficacy, like I said, four and a half years in some patients, we argue that mepolizumab is not therapeutically interchangeable with other asthma biologics, which is consistent with the recent GINA guidelines. Accordingly, GSK requests the committee maintain mepolizumab as a preferred medication on the PDL. Thank you, everyone. Happy to entertain any questions.

Lisa Chew: Thank you. Any questions? Okay. No questions. Thank you, very much. Okay. Let's move on to the motion. So, we first need to either approve the surveillance report as adequate or not adequate and wanting to request an updated class review.

Leta Evaskus: I just want to point out that I put dupilumab as a new drug, but it should be greyed out, because it's not eligible to be preferred.

Jordan Storhaug: I move that we determine the scan is adequate.

Catherine Brown: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. Let's move our attention to the motion. There is a prior motion there. It only talks about the treatment of asthma, not urticaria in the prior motion. So, we can either reiterate the prior motion or made edits.

Nancy Lee: I had a question about the second sentence, omalizumab is not included. And I was wondering if somebody can remind me why?

Leta Evaskus: I see all four are included.

Nancy Lee: In the second sentence it's not.

Leta Evaskus: Oh, here. Okay.

Nancy Lee: Yeah.

Lisa Chew: I'm not sure if this is right, but I wonder if it was because omalizumab had a prefilled syringe or something like that formulation that the others did not at the time?

Donna Sullivan: They have a different mechanism of action. So, I think that's why you're saying it couldn't be interchanged with the others.

Umang Patel: Just to tack onto Donna. So, the three that are listed there are all IL-5 antagonists. So, the can be interchanged. Xolair is an IGE antibody, so it cannot.

Nancy Lee: I propose that we continue, reiterate the prior motion.

Susan Flatebo: Should we add in that first sentence though, to the treatment of asthma and the chronic spontaneous urticaria?

Diane Schwilke: And we should add the new one that was discussed, too into the list, so there is five.

Lisa Chew: Because this is a surveillance report, we're not allowed to add new drugs to the PDL.

Donna Sullivan: Not all of these drugs are indicated for urticaria. So, we're reviewing this particular class right now, just for their asthma indication.

Jordan Storhaug: I think despite the concerns, I think it's still kind of new. So, I think we should just reiterate the prior motion.

Nancy Lee: I second that.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Okay. The motion carries. Okay. We're going to be moving onto atopic dermatitis agents' surveillance report. Beth Shaw, are you on the phone?

Beth Shaw: Yes. I am. Thank you. So, I'm going to present the report on drugs to treat atopic dermatitis. So, if we move onto the next slide, you can see it's the standard format that you've heard a couple of times already this morning. So, moving onto the background, atopic dermatitis, or eczema, is an inflammatory skin condition that affects around 30% of the U.S. population. That's mostly children and adolescents. Most people can achieve improvement and disease control with nonpharmacological intervention, conventional topical therapy, as well as environmental and occupational modifications. The newer biological therapies are really anticipated to provide an effective and safe longterm option to the patients who have a severe form of atopic dermatitis.

As we've heard, dupilumab is the first approved biologic treatment for atopic dermatitis; however, other biological treatments are in the research pipeline. I think there's some question about the role of individual topical corticosteroids and calcineurin inhibitors relative to each other. The question is how we use them. It's still evolving the role of the new systemic therapies. So, even though complex questions remain about the most effective therapies, the main [inaudible] of treatment [inaudible] and therapy for atopic dermatitis in people who are inadequately managed with topical treatment. I think there's also some concern about the safety of such longterm treatment and not specifically around the incidence of [inaudible].

So, just background on the history on the next slide. We can see here that the final report was published in December of 2017, and the searches for that report went through to September 2017. In that report, there was a network meta-analysis that compared effectiveness and harms using both placebo and active control trials.

So, in terms of the PICO, we were looking for both adults and children, as well as infants with stable atopic dermatitis. We were looking at the range of interventions, which you can see on the next slide. In terms of comparators, we were looking for the head-to-head comparators, as well as comparisons against topical corticosteroids. The outcomes, we were looking for response to treatment, symptom relief, quality of life, as well as adverse events.

On this next slide, you should be able to see now, the included interventions. Again, on the left hand side, we have the generic name. You can see the brand name, the drug class, as well as the route of administration, and the FDA approval information. I think it's worthwhile noting, again, that dupilumab approved in 2017 if administered through an injection. Whereas, the other three interventions that we're looking at in this report were topical administration.

So, on the next slide, here you can see the key questions. We were looking at both comparative effectiveness and harms, and we were also looking for any differences by subgroups. So, that might be patient demographics, comorbidities, or treatment duration.

On the next slide, you can see the methods. So, we looked for new drug formulations, indications, and serious harms or warnings. It was mentioned before using the FDA website and other websites. We used OVID Medline to look for new randomized control trials and systematic reviews. Then, we used trial registries to look for those ongoing studies.

So, moving to the next slide and the one after that would be the findings. There have been [inaudible] FDA actions, since that last report. We didn't find any new drugs, no new formulations, indications, or no new serious harms.

Moving onto the next slide, we didn't find any new systematic reviews, since the searches in the last report. However, we did find one new randomized control trial that compared pimecrolimus with topical corticosteroids and a placebo. We didn't find any randomized control trials for those other interventions.

On the next slide, you can see the characteristics of that single included randomized control trial. So, it was conducted in 30 adults with mild or moderate atopic dermatitis. It looked at pimecrolimus, compared with those topical corticosteroids and placebo. In terms of outcomes, they were looking for both disease symptoms, as well as molecular skin markers.

Next slide, please. You can see here in the ongoing studies, we identified four ongoing studies, two of which were active randomized control trials evaluating crisaborole in adults and children with mild to moderate atopic dermatitis, as well as two longer-term extension studies.

Next slide please. So, here's the information on those two included ongoing studies. The relatively large trial for populations of 600 and 160, both of them are due to complete in 2020. Again, a range of outcomes, such as response to treatment, quality of life, as well as anxiety, depression, and adverse events.

Moving onto the next slide, you can see the characteristics of these two extension studies. If you remember in the original report, they included only trial placebo or active controls, but we included them in these extension studies, but they don't have a comparator, but we have included them, just for information, because of that concern about longer-term safety of the new biologic therapies.

So, in summary, we found one new randomized control trial, two ongoing randomized control trials, and those two extension studies on dupilumab. Thank you.

Lisa Chew: Thank you, Beth. Any questions for Beth? Okay. There are no questions. Umang?

Umang Patel: Perfect. So, next atopic dermatitis, the topical immunosuppressants. Quick overview. So, atopic dermatitis, moving forward, is labeled as AD, is a chronic, noncontagious, inflammatory disease of the skin resulting from a combination of genetic and environmental factors. Often referred to as eczema, AD affects up to 25% of children and about 2 to 3% of adults. Roughly 70% of patients diagnosed have a positive family history of atopic diseases. Odds of developing AD are two to three times higher in children with one atopic parent and increase to three to five times if both parents are atopic. Although symptoms of AD can develop at any age, it is estimate that 60% of patients develop symptoms in the first year of life, while 90% develop symptoms before the age of 5. The majority of effected patients have resolution of the disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. Onset after age 30 is less common and is often caused by exposure of the skin to harsh or wet conditions. It commonly occurs in patients affected by asthma and other allergic conditions and is associated with elevated serum IGE levels. People who reside in cities and dry climates appear to be more likely to develop this condition. It is characterized by extremely dry, itchy skin on the insides of the elbows, behind the knees, on the face, hands, and feet. In response in terms of itching, patients may scratch or rub the affected area, which leads to further irritation and inflammation. As the skin loses moisture from the epidermal layer, it becomes increasingly dry and may begin to crack, weep, crush, and scale. This damage to the integrity of the skin renders it less protective and more prone to infection. Despite the chronic nature of this condition, there may be periods of the disease when the skin improves and periods when the skin worsens. Irritants, such as detergents, fumes, tobacco smoke, and alcohol containing skin products, and allergens like dust mites, pollen, and animal dander can exacerbate or cause ‘flareups.’

Moving to the next slide here, we have the indications. So, the medications here we have Eucrisa, Dupixent, Elidel, and Protopic. As I mentioned earlier, Dupixent is covered in this slide, because of the fact that it had two indications here. For FDA approved indications, Eucrisa is indicated for treatment of mild to moderate atopic dermatitis in patients 2 years of age or older. Dupixent is indicated for treatment of patients 12 years and older with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescriptions, therapies, or

when the therapies are not advisable, and it may be used with or without topical corticosteroids. Keep in mind, Dupixent is also indicated as add-on maintenance treatment in patients with moderate to severe asthma, age 12 years of age or older with an eosinophilic phenotype, or with oral corticosteroid dependent asthma. Elidel is approved for second-line therapy for short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older who have failed to respond adequately to other topical prescription treatments or when those treatments are not advisable. Lastly, Protopic is indicated as a second line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis or when those treatments are not advisable.

Just to give a quick mechanism of action to give you an idea of the pharmacology, Eucrisa is a PDE-4 or phosphodiesterase-4 inhibitor. It leads to increased intracellular cAMP levels. However, the specific therapeutic action of it is not well defined. Dupixent is an IL-4, which is found on both complexes resulting in inhibition of cAMP levels. Eladil binds to the intracellular protein macrophilin-12 and inhibits the calcium dependent phosphatase calcineurin, which inhibits T-cell activation by blocking cAMP. Protopic is a topical macrolactam agent. It's basically a complex flow line, which then binds to SKBP-12.

To continue onward, here we have the dosing and availability. As you can see, we have dosing stratified by adults and children. Availability varies from ointments to subcutaneous injections and creams, with Dupixent being the only prefilled syringe. In terms of pregnancy, just to give you extra information here, Eladil and Protopic are pregnancy category C. Pediatrics, as you can see, Eucrisa, Eladil, and Protopic have pediatric dosing and indication here.

On the next slide here, to give Dupixent its brief summary, as well. So, in October of 2018, FDA approved a new indication for add-on maintenance treatment of moderate to severe asthma in patients 12 years of age or older with an eosinophilic phenotype with oral corticosteroid dependent

asthma. Again, the dosing is stratified there. Availability as subcutaneous. There also is a Dupixent update in the web portal for the committee members, as well.

On the last slide here, we have the guidelines. So, according to the American Academy of Dermatology in 2014, it states that emollients, topical corticosteroid, and topical calcineurin inhibitors are the standard of care for treatment of patients with AD. For those whose eczema is not controlled by topical corticosteroids, or when there is a serious risk of adverse events from topical corticosteroids, topical calcineurin inhibitor should be used. Phototherapy is recommended as a treatment option after failure of emollients, topical steroids, and topical calcineurin inhibitors. Systemic immunomodulating agents are indicated for patients whose AD is not adequately controlled by topical regimens and/or phototherapy, and patients with this disease are prone to staph. Aureus infections and treatment with oral or topical antibiotics may be useful. According to the American Academy of Allergy Asthma and Immunology in 2012, they state Eladil and Protopic are reasonable treatment options for patients as second line treatment choices. Firstline include hydration, such as through emollients, moisturizers, and topical corticosteroids. Keep in mind that Eucrisa and Dupixent were not available at the time these guidelines were developed, but maybe considered as second line treatment options for patients with mild to moderate atopic dermatitis. Lastly, although topical corticosteroids are the standard of care in treatment, dermatologic effects, such as striae, atrophy, tachyphylaxis, as well as potential non-dermatological effects on linear growth rate, bone density, and hypothalamic pituitary, adrenal axis suppression limit the longterm use of these agents.

Lisa Chew: Thank you, Umang. Any questions? Okay. No questions. So, we have one stakeholder, Dr. Meredith Zarling. Again, please state your name and who you represent, and you'll have three minutes.

Meredith Zarling: Hi, thanks again, for giving me this opportunity to present to you. Again, my name is Meredith Zarling, and I am a medical science liaison with Sanofi Genzyme. We talked about already the indications for the only biologic that's approved for atopic dermatitis. So, we talked about that, Dupixent is approved for patients 12 years of age and older who have

moderate to severe atopic dermatitis. It can be used with or without topical corticosteroids and a calcineurin inhibitor. In the adult population, the approval in moderate to severe atopic dermatitis not adequately controlled with topical medications was based primarily on the results of three randomized double-blind placebo-controlled trials with a total of 2119 subjects who were 18 years of age and older. Trials 1 and 2 were Dupixent versus placebo with standard moisturizers. Compared to placebo, approximately four times more subjects taking Dupixent achieved almost clear skin. More than 40% of subjects taking Dupixent had 75% skin improvement. Trial 3 compared Dupixent with topical corticosteroids and placebo plus topical corticosteroids. Compared with placebo, the topical corticosteroids, nearly three times more subjects taking Dupixent plus topical corticosteroid achieved clear or almost clear, and nearly 70% of subjects taking Dupixent plus topical corticosteroids had 75% skin improvement. So, we talked about adolescent indication was approved earlier this year. That was based on the study that had 251 subjects aged 12 to 17, and also a safety and longterm extensive study was done. In summary, in both adult and adolescent subjects, Dupixent was superior to placebo in all efficacy endpoints whether you're looking at IgA score, which is looking at clearing of the skin to clear, which is 0 or 1, almost clear, and patients had to have a 2-point improvement. The proportion of patients with at least 75% improvement and the easy score from baseline and reduction from baseline to week 16 and itch, which was defined at least a 4-point improvement in the [inaudible] score. Most common side effects in adults and adolescents were injection site reactions and conjunctivitis. Thanks for your consideration. Again, I'd be happy to answer any questions.

Lisa Chew: Thank you, very much. Any questions? Okay. Thank you. Alright. So, let's move our attention to the motion. We need to first determine whether we think the surveillance report is adequate or not.

Catherine Brown: I move that we accept the surveillance report as adequate.

Susan Flatebo: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. The second item is to look at the prior motion and to decide whether we want to reiterate the prior motion or make a new motion.

Constance Huynh: I move that we accept the prior motion as stated, as reiterated.

Diane Schwilke: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries.

Leta Evaskus: Before we move on, I have two things. First of all, everybody with a binder, the HIV antiviral presentation was put under the last tab, DUR topic. So, if you can switch the contents of those two tabs. The other things is, Donna looked up here on our last class the asthma biologics that the original report, as well as this scan, did cover chronic spontaneous urticaria. So, we want to go back to that motion to see if you want to add in urticaria.

Constance Huynh: I move that we amend the previously approved motion to also add after treatment of asthma on the first sentence to also include chronic urticaria. Yes. Chronic spontaneous urticaria.

Lisa Chew: I'm sort of on the fence about this. There's not a lot of data. I know that one of the guidelines is, like, third or fourth line treatment, but I'd be interested in other committee members' thoughts about that.

Jordan Storhaug: That was my opinion, too, was that really we have some studies, but didn't really have any data presented, at least today, regarding their use for urticaria.

Lisa Chew: I guess I would rather not include urticaria here, but anybody want to make a comment about that?

Susan Flatebo: I agree. I think we should just reiterate the prior motion. Do we want to take a vote on that?

Lisa Chew: Does there need to be a second by anybody? I second the reiteration of the prior motion. All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Okay. The motion carries. Thank you for bringing that back up, Leta. Alright. So, we are now adjourning the P&T Committee and convening the Drug Utilization Review Board. Our topic will be HIV antivirals.

Umang Patel: Thank you. So, this class, there is going to be a lot of information here. It's going to be structured, unlike a lot of the classes I've given in the past. Just to give you a little bit of synopsis, these TCRs are updated semi-annually by Magellan. So, currently, HIV is in process of being updated. Therefore, Delvado, one of the newest medications, is not in this TCR, but it will be covered briefly by myself in the presentation, along with an NDU for Delvado is in the web portal for the committee to review. The second update is Descovy's newest prep indication that they just received about two weeks ago will be presented in the slides, as well. Dosing and availability that is historically provided for you is not going to be reviewed, but it's in the appendices at the end of this presentation if you wanted to take a look at any dosing or availability. The main focus on this will be guidelines and parameters. Okay.

Moving onto the background here. So, HIV, human immunodeficiency virus, is an infection that is a complex disease that results in destruction of the immune system of HIV infected individuals. There are two major subtypes. HIV-1, which is considered most responsible for acquired immune deficiency syndrome or AIDS pandemic, and HIV-2, which is thought to be less virulent and less transmissible; however, both are known to cause AIDS and are transmitted by sexual contact through blood and from mother to child. By far, HIV-1 is more common

worldwide, and HIV-2 is more concentrated in West Africa. The course of HIV infection varies, but the meantime from infection with HIV to development of AIDS related symptoms has been about 10 to 12 years in the absence of antiretroviral therapy, or ART, as I'll say moving forward. However, with the emergence of more virulent strains, time to AIDS progression may be getting shorter. Factors that influence the rate and severity of disease progression include age, genetic differences and the level of virulence of viral strain. Individuals infected with HIV with a specific mutation in the CCR-5 gene may have a slower disease course.

It was first identified in 1983, but it likely entered the United States in the late 1970's. Roughly 37 million people were living with HIV by the end of 2017 with 21.7 million receiving ART globally. In 2017, an estimated 47% of new infections occurred among key populations and their partners. From 1987 through 2015, roughly 507,000 deaths among people with AIDS in the U.S. have been reported by the CDC. It is estimated that only 75% of people with HIV know their status. Of new infection, approximately 68% are from male to male sexual contact, 23% from heterosexual contact, and 9% from injection drug use. The vertical transmission rate of HIV from mother to child has significantly decreased in the U.S. and abroad. A significant reason for this is associated with routine testing of pregnant women during prenatal care, and the provision of ART during pregnancy and delivery. Despite perinatal transmission being the primary means of child HIV infection, the risk can be reduced to less than 1% if recommended preventative measures are followed. The global decline in new cases coupled with an increase in survivability of HIV and AIDS has been attributed to the increased availability of ART. Access to effective prevention strategies and the improvement in care and support of those living with HIV and AIDS. The joint United Nations program on HIV and AIDS or UN AIDS in partnership with the World Health Organization has updated their strategy in hopes to end the AIDS epidemic by 2030. According to UN AIDS, 2016 to 2021 strategy, the target of 15 million people receiving HIV treatment by 2015 was reached nine months earlier than they had expected. Newly infected HIV patients dropped from 3.4 million to 1.8 million from 1996 to 2017, as well as a decline in the number of children acquiring HIV dropped by 35% from 2010 to 2017.

For the treatment of HIV, there are eight therapeutic classes that represent the drug treatment options. First being nucleoside and nucleotide reverse transcriptase inhibitors, NRTIs; non-nucleoside reverse transcriptase inhibitors, NNRTIs; protease inhibitors, or PIs; integrase inhibitors, INSTIs; CCR-5 antagonist; fusion inhibitors; pharmacokinetic enhancers; monoclonal antibody. Initial regimen selection should be guided by patient characteristics, including comorbidities, drug-drug interaction possibilities, toxicity risks, regimen complexity, and virological efficacy. Alternative regimens may be more desirable if individual patient needs warrant them. Alternative regimen identified by the consensus group are deemed efficacious, but may have select disadvantages compared to the preferred regimens.

On the next slide here, and roughly for the next eight slides, we'll go over different classes and their indications. Here, we have CCR-5 antagonist, Selzentry or maraviroc, and the mechanism for this is it exerts its activity by selectively binding on the CCR-5 receptor that is present on a cell membrane. So, it prevents an HIV virus interaction from occurring and entering the cell. Next, we have a fusion inhibitor, or Fuzeon, and the primary mechanism for this is through interference with the entry of the HIV virus into the cells by inhibiting the fusion of viral and cellular membranes by binding to the HR-1 receptor. Then, next we have integrase strand transfer inhibitors Tivicay and Isentress. These are basically HIV-1 integrase, as required for viral replication. The primary mechanism of these agents is through that integrase enzyme, which then prevents the integration and does not allow the HIV virus to replicate for these two. I'm not going to go through the indications for all of these, because when we get to the guidelines, we'll see what the recommendations are for starting alternative treatments for patients.

On the next slide here, we have NNRTIs, non-nucleoside reverse transcriptase inhibitors, which is composed of Rescriptor, Pifeltro, Sustiva, Intolence, Viramune, Viramune XR, and Edurant. And the mechanism for this is mainly by noncompetitively inhibiting the HIV-1 reverse transcriptase that blocks RNA dependent and DNA dependent polymerase activities, which does not allow the virus to replicate.

Next slide here, with the nucleoside reverse transcriptase inhibitors, we have Ziagen, Videx, Emtriva, Epivir, Zerit, and Retrovir. Again, these involve the inhibition of the reverse transcriptase that causes the termination of the DNA chain, which then does not allow the HIV virus to replicate, as well.

Pivoting over to the nucleotide reverse transcriptase inhibitor or NRTI, we have Viread, and the primary mechanism is through inhibition of both nucleotide analog reverse transcriptase and Hep B virus polymerase. It interferes with normal working of an enzyme, and it's essential, again, for a viral replication. We have a pharmacokinetic enhancer. So, that's cobicistat or Tybost. This is essentially... I like to refer to it as it's a sidekick. It's indicated in combination with atazanavir or darunavir to increase their systemic exposure once daily in combination with other ART for the treatment of HIV-1. So, essentially, it helps increase the pharmacokinetic enhancing effect of the elvitegravir by inhibiting the [inaudible] 3 enzyme.

Moving forward, we have the protease inhibitors, Reyataz, Prezista, Lexiva, Crixivan, Viracept, Norvir, Invirase, and Aptivus, and these help, essentially, cleave the viral polyprotein precursors, which through a long chain does not allow HIV virus to replicate. Keep in mind, ritonavir, Norvir inhibits both the HIV-1 and HIV-2 proteases. Then, we have recombinant monoclonal antibodies, or Trogarzo. This is a recombinant monoclonal antibody directed to domain 2 of CDR-4 T-cells blocking HIV-1 from entering the cell by interfering with the attachment steps.

So, we have those eight therapeutic classes. Now, we'll move to the combination products. So, we have, here you see Epzicom, which is abacavir/lamivudine. We have Trizivir, which is abacavir/lamivudine/zidovudine. Descovy, emtricitabine/tenofovir/alafenamide. Some duos, lamivudine/tenofovir/disoproxil fumarate; Combivir, which is lamivudine/zidovudine. Truvada, which is tenofovir and emtricitabine. Truvada is a name that has an extra indication for prep. I'm going to go over prep specifically in another slide, but just keep that in mind along with a new medication that's been approved. For Descovy, I did want to reiterate, so the limitation that's listed here for Descovy has been altered

in recent weeks. They received a pre-exposed or prophylaxis indication, and that is indicated in at-risk adults and adolescents weighing at least 35 kg for preexposure prophylaxis to reduce the risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV-1 test immediately prior to initiating Descovy. The limitation is used, as previously mentioned, the indication does not include the use of Descovy in individuals at risk of HIV-1 from receptive vaginal sex, because effectiveness in this population has not been evaluated yet.

Moving forward, we have continue combination products, atazanavir and cobicistat or Evotaz. Prezcobix, which is composed of darunavir and cobicistat. Kaletra, which is lopinavir and ritonavir. Keep in mind, Evotaz and Prezcobix are both coformulated consisted of a PI and a pharmacokinetic enhancer. Continuing with the combination products, we have Biktarvy, Symtuza, Triumeq, and Juluca.

On the next and final slide for the indications, we have the final slide of combination products composing of Delstrigo. We have Symfi and Symfi Lo, Genvoya, Stribild, Odefsey, Complera, and lastly Atripla. Now Atripla, Complera, Delstrigo, Odefsey, Symfi, and Symfi Lo are each coformulated with two NRTIs and one NNRTI. Biktarvy and Triumeq are an INSTI and two NRTIs. Genvoya and Stribild are coformulated consisting of two NRTIs and an INSTI, and a pharmacokinetic enhancer. Juluca is an NNRTI and an INSTI. Lastly, Symtuza is comprised of a PI, two NRTIs, and a pharmacokinetic enhancer.

As I mentioned earlier, the dosing and availability is available on the appendices. So, we'll skip right over that.

Moving over to Dovato. So, again, for Dovato, ANDU has been placed in the web portal if, if you would like more information. So, for Dovato, which is composed of dolutegravir and lamivudine, it is indicated as a two-drug combination, consisting of an INSTI and an NRTI, indicated as a complete regimen for the treatment of HIV type 1 infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual component. The contraindications are prior hypersensitivity to either component,

warnings are consistent with other antiretroviral combinations containing lamivudine and dolutegravir. These include boxed warnings for emergence of lamivudine resistant hepatitis B virus and the risk of post-treatment exacerbation of Hep B in patients coinfected. Additional warnings, again, are hypersensitivity, hepatotoxicity, embryo fetal toxicity, lactic acidosis, and hepatomegaly with steatosis. Dosage is listed there along with the availability. In terms of pregnancy, possible risk of neural tube defects has been associated with dolutegravir and due to limited knowledge of the types reported of that neural tube defect, avoid use of Dovato at the time of the conception through the first trimester of pregnancy. In terms of pediatrics, safety and efficacy have not been established. For hepatic impairment, there is no dose adjustment needed in patients with mild or moderate hepatic impairment, but it is not recommended for severe hepatic impairment.

Moving onto the guidelines. So, there are numerous guidelines for different population types here. The first being DHHS, the Department of Health and Human Services from 2018. The updated October 2018 guidelines for adults and adolescents continue to recommend initiating ART in patients with acute and recent HIV-1 infection, regardless of CD-4 cell count under the evidence rating of A1 being the strongest it can be. The recommendations are strongly based on findings from two large studies, the Start and the Temprano studies that demonstrated a 50% reduction in morbidity and mortality among HIV infected patients with CD-4 cell counts greater than 500 cells/mm2. Although these studies do not include adolescents, the recommendation to initiate ART therapy early has been extended to this population. ART is recommended for all persons with HIV to prevent transmission and reduce the morbidity and mortality regardless of CD4 lymphocyte cell count. In select patients, ART may be deferred due to clinical and/or psychosocial factors; however ART should be initiated as soon as possible. Patients who are considering ART should be well informed of the risk and benefits of both treatment and postponing treatment in order to make an informed decision. Possible therapeutic complications from non-adherence or adverse reactions need to be considered by the patient to ensure commitment, once treatment has started. The only individuals who are generally not recommended for ART are those unwilling or unable to commit to treatment. According to the International AIDS Society, IAS, in 2018, they recommend HIV drug

resistance states that although ART has diminished HIV treatment failures, overall transmission of the virus has not diminished. Therefore, IAS continues to recommend testing for HIV drug resistance in drug naïve individuals and in patients in whom ART is failing, as this can play a pivotal role in preventing and managing resistance.

Continuing with the DHHS guidelines, they recommend that CD4 counts be measured every three to six months during the first few years of therapy. If viremia develops while patient is on ART, the initiation is delayed. If there are ART modifications and CD4 count reaches less than 300 cells per mm2, testing is then recommended to be every 12 months after two years on ART with a consistently suppressed viral load. Drug resistance testing is recommended at entry into care, regardless of whether therapy will be initiated immediately or deferred. They also recommend mutation testing for reverse transcriptase, protease genes, and INSTIs if needed. If therapy is deferred, repeat testing should be considered at time of therapy initiation. Resistance testing is recommended in the setting of virologic failure while the patient is taking the drug, or within four weeks after discontinuing therapy. If more than four weeks have lapsed, since discontinuation, resistance testing may still provide useful information to guide therapy. Now, in terms of genotypic testing, as described above, it should be employed to detect resistance. In patients who are experiencing treatment failure and for whom conventional HIV RNA genotype drug resistance testing is unavailable or unsuccessful, next generation sequencing resistance assay that involves proviral DNA can be considered. It is imperative to interpret these results with caution, as these assays can miss some or all of previously-existing drug resistance mutations. When such testing is obtained, results should be combined with all prior genotypic and phenotypic test results to construct a cumulative genotype, which will incorporate all current and previously detected mutations. It is important to note that the usefulness of these assays in a clinical setting is still under investigation as yet to be fully determined. So, please take with a grain of salt there. A proviral DNA tropism assay can be utilized for patients with undetectable HIV RNA when a CCR5, such as maraviroc, is considered for use in a new regimen, such as part of a regimen switch or simplification. The guidelines recommend that for treatment experienced patients with multidrug resistant HIV, the clinician should consider enrolling the patient

in a clinical trial of investigational drugs, or contacting pharmaceutical sponsors that may have investigational agents available. Hemoglobin A1c, HIV serology, and hep C serology testing are also recommended, and they are broken down by timeline in the TCRs. Notably, patients should be screened for both hep B and hep C at entry into care, as having the coinfection may impact the initiation of ART's.

By the IAS, they state that the HIV testing is recommended at least once for anyone who has been sexually active, or more often for individuals that are at ongoing risk of infection. They conclude that after a confirmed diagnosis, ART should be started as soon as possible, including immediately after diagnosis, regardless of the CD4 cell count. Samples of the HIV RNA level, CD4 count, genotype for NRTI, NNRTI, PI, lab tests, such as active hepatitis, chemistry should be drawn at the beginning of the ART treatment, but treatment may be started before the results come back. Results for HLA-B 5701 allele should be available if an abacavir containing regimen is anticipated. Regimens should be selected or changed, based on resistance test results with consideration of dosing frequency, pill burden, adverse events profile, comorbidities, and drug interactions. Patients receiving ART should be monitored regularly and treatment failure should be detected and managed early with the goal of therapy, even in previously-treated patients being HIV-1 RNA suppression below commercially available assay quantification limits. Furthermore, if they indicate that an INSTI plus two NRTI's is generally recommended for initial therapy with unique patient circumstances. We will go into starting an alternative treatment soon. NNRTI's and abacavir should not be used for rapid ART start. The group states that tenofovir is not recommended for individuals who are at risk of kidney or bone density; however, if it is not available, or if there is a substantial cost difference, tenofovir with emtricitabine or lamivudine is effective and generally well tolerated. Again, a CD4, HIV RNA genotype, and other lab tests for general health and coinfections are recommended, as specified points again in the TCR. Lastly, if a regimen switch is indicated, treatment history, tolerability, adherence, and drug resistance should first be assessed. Two to three active drugs are recommended for a new regimen.

So, going onto starting. Again, just to break it down into columns. So, the IAS recommends initial antiretroviral treatment of adults that is broken down into either INSTI's plus two NNRTI's, and the treatment options are below. NNRTI's plus two NRTI's, which you have two options there, and ritonavir boosted protease inhibitors plus two NRTI's.

I should have mentioned this earlier. A lot of these medications, not only do they have generic, not only do they have brand, but they also have a three-letter code. The three-letter code should be on the indication slide, as well. So, if you have any questions about that, please let me know.

Continuing on with guidelines, the DHHS continues on to say that before starting dolutegravir and other integrase strand inhibitors as initial therapy, pregnancy testing should be performed in those of childbearing potential, prior to the initiation, due to preliminary data showing increased risk of neural tube defects in infants born to women who are receiving dolutegravir. It should not be prescribed for the following individuals, those who are pregnant, and within 12 weeks post conception, patients of childbearing potential who are planning to become pregnant, and those who are of childbearing potential, are sexually active, and are not using effective contraception. For those who are using effective contraception, dolutegravir can be considered after weighing the risks and benefits. In addition, patients who are pregnant, bictegravir is not recommended, due to insufficient safety data and elvitegravir/cobicistat combo is not recommended, due to reportedly low elvitegravir plasma concentrations during the second and third trimester. There is limited raltegravir data during the first trimester in the U.S. Currently, it is not known whether the link between dolutegravir and neural tube defects represents a class effect; however, the potential risk should be discussed with the patient of childbearing potential who prefers an INSTI containing regimen.

So, then, according to the DHHS guidelines, here you have on the top treatment options for most treatment naïve adults and individuals. INSTI based regimen, and they say most, because I just went into why you wouldn't want to start someone on an INSTI, along with coformulated product availabilities on the right hand side. Then, below, we have

alternative or other treatment options in treatment naïve adults and individuals, again, recommended for certain clinical situations. INSTI based, NNRTI based, protease inhibitor based, and the coformulated products that are available on the right hand side.

Moving forward here, continuing with the DHHS guidelines for preferred treatments for treatment naïve children and adolescents, this is stratified by age. So, infants from birth to age less than 14 days, two NRTI's plus nevirapine or raltegravir is recommended. Children 14 days or older, postnatal, and up to 3 years, two NRTI's plus lopinavir and ritonavir or raltegravir are recommended. Children 3 years of age up to less than 6 years, two NRTI's, atazanavir and ritonavir, darunavir and ritonavir, or raltegravir are recommended. Then, 6 years to 12 years, two NRTI's plus atazanavir and ritonavir combo, or dolutegravir. For dolutegravir, it can only be for children/adolescents weighing 30 kg or more. Adolescents 12 years of age or older is broken down with two NRTI's with atazanavir an ritonavir, dolutegravir, again weighing over 30 kg, darunavir and ritonavir, or elvitegravir/cobicistat combo, again weighing greater than or equal to 35 kg.

Continuing on here, I won't go onto these. These are alternative regimens for treatment naïve patients for children and adolescents if the preferred are not applicable.

Continuing on, for pediatric recommendations, the preferred two NRTI backbone treatment naïve children and adolescents, so this is kind of zooming in on those two NRTI's, which NRTI's they would recommend, and alternatives.

Alright. And then, the last slide here for DHHS recommendations are for pregnancy recommendations. So, initial combination regimens for antiretroviral naïve pregnant women, two NRTI backbone options. There are three options there. We have a protease inhibitor based regimen, two options there, as well, and then an INSTI based regimen. Keep in mind, dolutegravir, again, I keep emphasizing this, is not recommended for use in first trimester. Alternative treatment options are below.

Lastly, as promised earlier, PrEP – so pre-exposure prophylaxis. Now, daily oral pre-exposure prophylaxis has been shown to be safe and effective in reducing the risk of sexual HIV acquisition in adults. Therefore, PrEP is recommended as one prevention option for sexually active men who have sex with men, MSM, at substantial risk of HIV acquisition, adult heterosexually active men and women who are at substantial risk of HIV, adult persons who inject drugs at substantial risk of HIV. PrEP should be discussed with heterosexually active women and men whose partners are known to have HIV infection. Before prophylaxis is initiated, clinicians should determine eligibility for PrEP by ensuring the individual is HIV negative at high risk for acquiring the infection and has a calculated creatinine clearance of greater than or equal to 60 mL/minute. It is advisable to evaluate sexual partner therapy status, pregnancy lactation status, acute HIV infection symptoms, and screen for comorbid conditions, such as hep B and STI, sexually transmitted infections. It is recommended to conduct STI testing in sexually active persons with signs or symptoms of infection and asymptomatic MSM at high risk for recurrent bacterial STI's. Those with syphilis, gonorrhea, or chlamydia at prior visits, or multiple sex partners. The updated CDC guidelines state that for gonorrhea and chlamydia testing in MSM, pharyngeal rectal and urine specimen should be collected. It is dubbed as a three-site testing to maximize the identification of infection, which may occur at any of these sites at exposure during sex. No more than 90 days of PrEP should be prescribed initially. Subsequent dosing relies on followup HIV test being negative, since there is a high risk of antiretroviral resistance developing if the regimen is used while HIV infected. Non-adherence to the regimen is another criterion for discontinuation. It is critical that education be provided to the user on both pharmacological and nonpharmacological means to minimize the risk of HIV transmission. Individuals who become infected should discontinue PrEP and be offered a preferred antiretroviral treatment regimen. Transgender persons are those who sex at birth differs from their self-identified gender. Although the effectiveness of PrEP for transgender women has not yet been definitively proven in trials, and trials have not been conducted among transgender me. PrEP has been shown to reduce the risk of HIV acquisition during anal sex and penile vaginal sex. Therefore, its use may be considered in all persons at risk of acquiring HIV sexually. Just to reiterate, there are now two medications that are FDA approved for PrEP, Truvada has been the

hallmark for a few years now, and roughly about two-ish weeks ago, Descovy.

Lisa Chew: Thanks, Umang. You can take a rest now. Does anybody have any questions?

Donna Sullivan: We do have... we invited an HIV expert. So Shonna Aplin from Tacoma to come up. So, Shonna can answer any questions that you might have about the HIV regimens.

Lisa Chew: Welcome. Anybody have questions for Shonna? Perhaps later. Should we go through the policy and then stakeholders?

Female: I do. I wonder if Shonna could share just a little bit about the difference in PrEP regimens with the new approval? I don't know if there's anything there to share there.

Shonna Aplin: Sure. So, Truvada for PrEP has been out for quite a while. Then, as he mentioned, Descovy was just approved last week. The difference is the tenofovir component. So, it's the old Truvada is tenofovir disoproxil fumarate. That's the one that has some connection with bone mineral density loss and potential for a fanconi type syndrome. So, the new version, Descovy, has tenofovir alafenamide, and that is more neutral when it comes to the kidneys and the bone. We've been using it on the treatment side for many years, but that's the main difference in the compound, itself, but also there is an FDA indication that is different for Descovy for PrEP compared to Truvada, because the trial, the Discover Trial that studied Descovy for PrEP did not include cisgender women. So, the FDA didn't feel like there was enough data to approve it in insertive vaginal sex. So, your over… this is perfect for PrEP, in general, but there's a little different in the indication that if someone is HIV risk sexually is receptive vaginal intercourse, then Truvada would be the one for them to use versus if the penis or the anus is the risk factor. Then, either one is FDA approved.

Omar: This is Omar from CHPW, just a quick question for Shonna around any recommendations that came out, or any differences between protocols for initiating folks on Truvada versus Descovy for PrEP. Any sort of

guidance differences, as far as kidney function, looking at any other factors in making the decision to initiate a patient on either?

Shonna Aplin: Yeah. Thank you. That actually reminds me of something else. So, the creatinine clearance minimum for Truvada is 60. It can go down to 30 with Descovy. So, if you have a patient with chronic renal disease that would be another reason you would choose Descovy over Truvada, but back to your question about monitoring and that kind of thing. It's much more lax with the renal monitoring, because of the safety, but initiation wise, if you assess risk, get them on PrEP, right, whether it's Truvada or Descovy. There was no difference in any of that guidance.

Donna Sullivan: So, tone of the recommendations that we were... or changes in the recommendations, and we can look at the preferred drugs, as well, was that all the products are considered safe and efficacious and are eligible to be preferred, and that grandfathering and preferred status be at the discretion of the Health Care Authority, and that all nonpreferred products require trial of only one preferred product. So, previously, we required a trial of two products. So, we're changing our recommendation to only one product that has the same indication before a nonpreferred drug would be authorized, unless there's contraindications or clinical reasons why they can't the preferred products. So, I want to then just segue to what is preferred. So, this is our HIV class. It's a little noisy, because we have a lot of the generics of the single ingredient products. It's not in your spreadsheet. So, that's not the spreadsheet that you have. I apologize for the confusion, but if you want to see the products that we do have preferred, we have Tivicay preferred, which is indicated for treatment in combination with Descovy. We have Stribild. I was trying to go through and highlight some of these, as we were looking at the classes. It might be easier to show you what's not preferred, because there's fewer products. So, at this point in time, really, the only things that are not preferred are things that have a generic available, or some of the newer combinations that have come onto the market. So, they are... I can filter them out for you. So, Biktarvy, Symtuza, Dovato, Juluca, the Delstrigo, Symfi, [inaudible]. I'm not sure how to pronounce that one, and Norvir. There's generic ritonavir that is preferred. So, these are the products that are not preferred. We do have several firstline agents that

are recommended by the guidelines that are preferred. Those are the ones that I had highlighted.

Shonna Aplin: So, I don't know your first name. Is it Umang? When Umang reviewed the DHHS recommended guidelines, if you didn't notice, all the recommended agents are from the integrase class. So, they have really actually changed from being covering lots of classes to really we've hone into this one class. The reason is, it's very well tolerated, a small number of pills, few side effects, things like that. So, my comment is in the list that Donna just gave, there is one of the four DHHS recommended regimens that is not on the preferred formulary for Medicaid, and that's Biktarvy. The other three of the four recommended regimens are a part of that. So, clinically, it would be something... I wouldn't ask for all HIV medications in any way to be added to the formulary. I don't think that's appropriate or a good use of money, but just looking at what would guide what should be a preferred regimen clinically what we use is the recommended regimens from DHHS. So, could that be a consideration of using that as your decision making and including that one along with the other three, just because it is on your preferred regimens from the DHHS.

Lisa Chew: Thank you. Any questions for Donna or Shonna before we move to stakeholders? Okay. We have six stakeholders. So, the first on is Dr. Terra Stone. After that will be Aaron Huwe. I'll just kinda list two at a time. State your name, who you represent, and you will have three minutes for comments.

Terra Stone: Good morning. My name is Terra Stone. I'm a medical science liaison for VIIV and certified through the American Academy of HIV Medicine. I am here for your consideration of Dovato. Dovato is dolutegravir, which is an integrase inhibitor, and 3TC, which is an NRTI, the first complete two-drug single tablet regimen for the treatment of naïve HIV patients. The efficacy and safety of Dovato were demonstrated in two trials in over 1400 subjects. Dovato was shown to be noninferior to dolutegravir three-drug regimens out to 96 weeks. Both dolutegravir and 3TC are on the WHO list of essential medications. Agents can successfully suppress the HIV virus when patients are adherent. It is equally important to tackle antiretroviral treatment or ART, longterm toxicities, when possible. 24 to 34 is the average age of diagnosis here in Washington in 2017.

These patients can potentially live on ART's for 30 to 40 years. The FDA Dovato press release stated, "With this approval, patients who have never been treated have the option of taking a two-drug regimen in a single tablet while eliminating additional toxicity and potential drug-drug interactions from a third drug. Comorbidities in people living with HIV and communicable drug exposure are becoming more evident, as this population ages. Dovato is both abacavir and tenofovir free. Surrogate renal function and bone turnover markers were all significant in favor of Dovato. Using individual components instead of a single tablet regimen may lead to increased risk of resistance and transmission, concern for both patients and for public health. There is evidence that single tablet regimens lead to better patient outcomes. Dovato was noninferior to dolutegravir base 3 drug regimen when no treatment emergent resistance and had fewer drug-related adverse events with the Dovato arm. Thank you for your attention. I hope that you will consider moving the treatment of HIV forward by including Dovato as a treatment option for patients. I would be happy to take any questions.

Lisa Chew: Thank you, Dr. Stone. Any questions? Okay. Thank you. The next person is Aaron Huwe. Then, following that will be Michelle Puyear.

Aaron Huwe: Good afternoon. My name is Aaron Huwe. I am a medical affairs director with Merck and happy to be here today. I wanted to provide the committee with relevant information regarding Pifeltro, otherwise known as doravirine. Pifeltro is a non-nucleoside reverse transcriptase inhibitor. It is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients. With no prior treatment history or in the last two weeks we also had an updated label expansion to also replace current antiretroviral therapy in those patients who are virologically suppressed, on a stable anti-ARB regimen with no history of treatment failure, and no known substitutions associated with resistance to doravirine. So, that's one key update. Doravirine is also available as Pifeltro, which is a single NNRTI to be used in combination with other antiretrovirals, and also as Delstrigo. A fixed dose single-tablet regimen containing doravirine, lamivudine, and tenofovir. Pifeltro is contraindicated when coadministered with drugs that are strong, Syf-3450 [sounds like] inducers significant decreases in plasma levels may occur, decreasing the effectiveness of [inaudible]. The efficacy of Pifeltro

is based on analyses of 48-week data from two randomized multicenter placebo controlled trials, Drive Forward and Drive Ahead. This was specifically studied in those patients with an HIV-1 infection with no antiretroviral treatment history. Drive Forward included 766 subjects, who were randomized to receive at least one dose of either Pifeltro once daily or boosted darunavir plus ritonavir daily in combination with FTC TDF or ABC 3TC as selected by the investigator. In Drive Head, 728 subjects were randomized to receive at least one dose of Delstrigo or efavirenz containing regimen, which is essentially the components of Atripla. The 48-week data for Drive Forward essentially resulted in an 84% of patients achieving an HIV RNA of less than 50 copies, as compared to the boosted darunavir group, which was similarly at about 80%. When we looked at the Drive Ahead results, 84% of patients on Delstrigo achieved virologic control compared to 81% of those folks on Atripla. The efficacy was independent of baseline factors, including CD4 count and high viral load in both trials. Doravirine, as such, was noninferior to the comparator in terms of CD4 count and also HIV RNA levels. The most common adverse events were nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, and abnormal dreams. In general, the incidents of resistance is very low, about 1.1% with doravirine. It does have a unique resistance pathway in terms of the substitutions versus the traditional NNRTI mutations. Doravirine, in closing, has minimal drug-drug interactions. It can be taken with proton pump inhibitors, metformin, iron-containing agents, oral contraceptives, and most importantly, can also be taken without respect to food. Finally, as of the October 25th DHHS guidelines, doravirine is now listed as an alternative therapy, and I thank you for your time. I am happy to entertain any questions.

Lisa Chew: Thank you, Aaron. Any questions? Okay. Thank you. Michele Puyear, and after that will be Mae Kwong.

Michele Puyear: Good afternoon. My name is Michele Puyear. I am a medical scientist with Gilead Sciences. I am here today to talk a little bit about HIV and specifically about Biktarvy. Over the next couple minutes I wanted to hit three things that may impact the State's initiative to end AIDS. That is Rapid Start adherence and how a single tablet regimens, or STR's, can impact adherence, and then how Biktarvy fits in. If you're not familiar

with the End AIDS campaign, one of the goals is to decrease the... or increase the number of patients who are virologically suppressed, which is really important, because we know treatment as prevention. If you're suppressed, you won't spread HIV, which is really important for the other goal, which is to decrease the number of new infections by 50%. One of the initiatives that you see around the country is called Rapid Start, which means you get patients on treatment as quickly as you can after they're diagnosed. Sometimes, even on the very first day of diagnosis. They are not... all agents are not appropriate for Rapid Start, but Biktarvy is one of the agents that the guidelines say can be used or considered for use of Rapid Start. The next is adherence. Adherence is very important, because you can't get patients virologically suppressed, unless they are adherent. There have been two studies this past year that have looked specifically at the Medicaid population and the impact of single tablet regimens versus multi-tablet regimens and adherence. One was published by Express Scripts. The other one was published in the Journal of Managed Care Pharmacy and looks at the Magellan population. Overall, they found that patients on single-tablet regimens were more adherent versus patients on multi-tablet regimens. Some of the other unique things that they found were... something that's not unique is that Medicaid patients had a higher pill morbidity burden, and particularly in the Magellan population, they saw almost a quarter of patients had major depressive disorder. The other thing that they found was that even patients starting out new to treatment on multi-tablet regimens, almost 50% of them were nonadherent within the first 15 months. So, we know how important adherence is. The last part is, and why Biktarvy. Where does that fit in? As was mentioned earlier, Biktarvy is a single tablet regimen. When you're considering agents to treat patients, obviously you want a product that can have high virologic suppression, high barriers to resistance, it needs to be tolerable so patients are staying on, so low adverse events, and then the part about being a single tablet regimen is very important, and also being to take it with or without food. So, Biktarvy fits all of that criteria. And as you've already heard, it is recommended by the guidelines, as a preferred regimen for most patients who are starting out and new to treatment. So, as you're considering all of these agents, consider how this would impact your state's ability to get to its goals of ending AIDS. Thank you.

Lisa Chew: Thank you, Michele. Any questions? Okay. Now, Mae Kwong and followed by Scott Bertani.

Mae Kwong: Good afternoon. My name is Mae Kwong with Janssen Scientific Affairs. I will be discussing Symtuza today. The first and only protease inhibitor based complete single tablet regimen that contains darunavir. Darunavir is important, because it is the only protease inhibitor with an A1 recommendation in the DHHS guidelines. For certain clinical situations, such as certain adherence or the need to start antiretroviral therapy before drug resistance tests are available. For instance, as I just mentioned, Rapid Start of therapy, or rapid initiation of therapy. After ten years of studying darunavir in clinical trials, loss of susceptibility has never been observed, and among the three trials supporting Symtuza, no patients developed darunavir resistance. Darunavir was first approved in 2006, and after 13 years on the market, it has proven to maintain its high genetic barrier to resistance. Based on 2018 Washington Department of Health statistics, there are over 13,000 patients living with HIV. From 2012 to 2016, over 450 new diagnosis each year. Real world analysis show poor adherence rates for antiretroviral therapies are high in Washington State, upwards of 41%, and in the Seattle area, as high as 73%. Resistance rates within Washington are upwards of 29%, and in the Seattle area anywhere from 31 to 40%. The World Health Organization and the International AIDS Society recommend rapid initiation, or Rapid Start, which is starting HIV therapy upon diagnosis and prior to having resistance testing. Rapid initiation has been shown to lead to improved virologic outcomes, retention in care, decreased mortality, and decreased transmission of HIV. Symtuza is the only single tablet regimen with data from a phase-3 study successfully employing rapid initiation. In the Diamond phase-3 study, 96% of patients were virologically suppressed at week 48. Symtuza once daily complete regimen is a first and only PI based single tablet regimen that contains the high genetic barrier to resistance of darunavir, the safety and tolerability profile of tenofovir alafenamide, a single tablet regimen to improve adherence, as well as phase-3 supporting data for rapid initiation. Real-world data also shows that cost per patient increases on later lines of therapy, and rapid initiation has longterm economic benefits for Medicaid patients. For these reasons, I ask that Symtuza be added to the Washington PDL as a preferred agent and made available for Washington Medicaid patients

while removing the need to fail prior therapies or prior authorization, which would prohibit rapid initiation. Thank you.

Lisa Chew: Thank you, Mae. Any questions? Okay. Scott Bertani followed by Dennis Torres.

Donna Sullivan: Dennis just signed up thinking that was a sign-in sheet. So, he's not going to be testifying. Thank you.

Scott Bertani: Hi. My name is Scott Bertani. I am here representing Lifelong AIDS Alliance, Pierce County AIDS Foundation, Hepatitis Education Project, Cascade AIDS Project, as well as Entre Hermanos. That's roughly about 3200 clients in the state of Washington, which is about a third of all individuals who are diagnosed with HIV in this State. As I look across the room, it's really to see so many familiar faces here at the table coming together to talk about this class review, because two years ago I was the only individual who made mention about this new class review on July 7th, 2017, and I think then, as you know, there have been many FDA approved medications and regimens that have come online. You've all been, reviewed them today. The concern that we have is that a two-year gap before another review raises some significant issues in how this board creates processes, protocols, or even best determines clinical care standards of care for the dispensation of antiretrovirals. I mention that, because I see that there is already a motion that makes mention that you move from a twice fail therapy to a once fail therapy for nonpreferred medications, even before the provider or community input was added. So, I think that sets some type of chasm amongst individuals that are on Medicaid who are often the poorest of the individuals that you are already determining for them before we who are those who represent them for medical case management and work with the providers even have the opportunity to weigh in on these discussions. I think that sets a dangerous precedent, not just the process and protocol, but what happens when there is new biologics or new immunologics that come online? Will we wait another two years before this process happens? Or will we have conversations behind closed doors. That's a concern that I have. I mention that also because I'm the past immediate co-chair of the HIV planning steering group who has worked tirelessly over the course of my 16 years in this State for the End AIDS Washington initiative to even

get online. We really applaud this Board having conversations with the HBSG provider community, but there are many of us who still have some differences, so to speak. As you know, there's many examples that include in studies that say that step therapies are not good ideas for individuals who can communicate a virus onto another, especially these communicable diseases, and that single-tab regimens are obviously one of the best primary choices for individuals. So, it seems that for individuals who would be placed on the State Medicaid options that are constricted into these plans, that you should have the availability at minimum the single-tab regimen so that people are not having pill burden. Think about individuals that are on these Medicaid plans, they are often individuals with high acuity, high utilization. They're often potentially in and out of Emergency Rooms. They may not have a home. Where will they keep their three pill bottles when they're out looking for work or for their provider or whatnot? You shouldn't do that. So, a single-tab regimen is important to have. We recognize that in May 2019, the Medicaid CMS had stated that protected classes for Part D should include all access to antiretrovirals, and we know that there's some dissimilarities here, but what we're creating is a potential chasm between those who have employer-sponsored plans, or ADAP, versus those individuals who are on the Medicaid PDL, and our clients, like I said, we represent about 3200 clients. This is not the way that we had hoped this would go, especially when the BREE Collaborative of which I served on, had made recommendations for minority sexual health to include clinical care standards. So, I would suggest to go back even and review the letter that was sent from the Health Care Authority to the Department of Health suggesting that there is a new progressive idea. Having a once fail is a better bad idea. I would suggest that you rereview this and take this into consideration. I'll get off stage.

Lisa Chew: Thank you, very much, Scott. Any questions for Scott?

Donna Sullivan: I just want to make a statement. We did not make a motion before we took stakeholder input. We just gave you a recommendation. So, there is no motion on the table.

Lisa Chew: Okay. So, let's look at the recommendation here. Actually, Donna, could you tell us what the Department of Health HPSG?

Donna Sullivan: Yeah. So, it's the provider group, I believe that the gentleman just referred to. It's the HIV, Kerrie, can you help me? Planning and Steering Group, clinical advisory committee. So, I met with them about a month ago, and we started talking about this particular class, which is why I agreed to... we put it on the agenda for review. There was a lot of conversation about whether all of the drugs needed to be preferred or not preferred, specifically, when there is a significant difference in cost between the firstline recommended regimens. When you're initiating treatment, should you be initiating treatment in a treatment naïve patient with the recommended drug or regimen that cost the least amount? You won't know if they're going to respond, or how they're going to respond until you actually try it. We've gone through this with many other classes, the antipsychotics. So, we're just asking to be able to prefer lesser expensive products that are still clinically appropriate and recommended by the guidelines. One of the conversations is that one of the preferred drugs, if we could only have to try one regimen before they try a nonpreferred regimen that would be preferable. Not all of the drugs needed to be preferred. So, this is where this recommendation came from, and we are willing to... we don't... because the DUR Board typically does not discuss cost when they're making our motions, we don't discuss that with you, as we're picking the preferred drugs. Our process would be to based on your recommendation go do a cost analysis and then looking at the guidelines. That's why we said in consultation with this advisory group that we will make a determination of which will be the preferred drugs. We will also be looking at recommendations for therapy for PrEP therapy now that we have a second medication that has received FDA approval, and that Truvada is actually off patent, and we expect a generic version of that particular product soon. So, we'll be working with this clinical advisory committee to develop those policies and bring them back, but for consideration of the PDL, we're hoping to get a recommendation that gives us the latitude to do the cost analysis and then look at the guidelines and pick the appropriate preferred products.

Lisa Chew: So, the list that you showed us earlier, was that just what the current state is, and that you're going to relook at that list/

Donna Sullivan: Correct.

Lisa Chew: And determine what's preferred and not preferred? Okay. Thank you. So, the committee needs to make a motion whether we want to go with this recommendation and vote on that.

Donna Sullivan: So, this is Donna. So, for ease of having a motion, if you agree with the recommendation, I did put it into a motion format. If you want to read it or if you want to edit it in any way, that's why we're here.

Nancy Lee: I would like the committee to consider adding in, let's see, in consultation with the Department of Health HPSG Clinical Advisory Committee and current clinical guidelines.

Lisa Chew: Any other suggestions in terms of editing the motion there?

Virginia Buccola: Would it be helpful for HIV agents to be amended to make a statement about prevention? I know they're the same, we're talking about the same class of drug.

Donna Sullivan: So, this is Donna. It, we typically don't make the class, break the classes out by their indications, because some have multiple indications. Some only have a single indication. If you want to say that we need to have a PrEP product preferred, then, you know, that's your prerogative.

Lisa Chew: I like the motion. I think it gives you the guy's latitude and tapping into experts and clinical guidelines and kind of creating the preferred and non-preferred drug list. So, I move that all products in the antiviral HIV agent drug class are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of HCA in consultation with the Department of Health's HPSG clinical advisory committee and current clinical guidelines. All nonpreferred products require a trial of one preferred product with the same indication before a nonpreferred drug will be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Susan Flatebo: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. I think it's lunch. Let's see, 30 minutes should we say. Like, just 12:55? Okay.

Donna Sullivan: We're going to review some of our clinical policies. We're kind of changing the format of how we do it to kind of improve efficiency. So, instead of having a slide presentation going through what the criteria are, which can sometimes get translated incorrectly into the policy, we're actually just going to go through the policy in the Word document, and we'll just make edits as we go along if you have any changes that you feel we should be making. So, the first policy that we're going to look at is for the monoclonal antibodies anti-IGE antibodies, and specifically the medication is Xolair.

So, as a general statement, the note at the top, when we have our policies, if a new indication comes out onto the market after we've approved the policy, we are basically stating that any requests for that new indication will be reviewed according to the FDA label. Nonpreferred drugs in this category require the trial of the preferred drugs, as well, for a policy. So, if somebody is requesting authorization for a nonpreferred drug, they still have to go through the preferred product process also.

So, our background is, you know, asthma we know is chronic inflammatory disease. Umang went through the clinical mechanisms for this medication. So, our PA policy was really to, for Xolair, would be for severe persistent allergic asthma in patients 6 years of age and older that have a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids, or that they have chronic idiopathic urticaria in patients 12 years of age and older who remain symptomatic despite the antihistamine treatment. So, and our policy is that Xolair would not be considered medically necessary when used for relief of acute bronchospasm or status asthmaticus, treatment of other allergic

conditions, or other forms of urticaria, or treatment of atopic dermatitis. Any questions about Xolair?

Now for the next indication. So, for moderate to severe persistent allergic asthma, it would be uncontrolled or inadequately controlled severe persistent asthma defined by the following: FEV-1 less than 80; two or more bursts of systemic corticosteroid in the previous 12 months, and that should say oral or systemic; frequent [at least twice per year] additional medical treatment, such as an ER visit or hospitalization; unplanned absences; limitation of activities of daily living; nighttime awakening or dyspnea. Poor control, which is greater than 1.5 or the ACQ score consistent less than 20, and they have a history of failure of at least six weeks or contraindications or intolerance to the medium to high dose inhaled corticosteroids. They have the positive skin prick test to one or more allergens, which support the patient's clinical history. They have a pre-treatment serum IGE level between 30 and 1500 IU/ml. There is combination use with other monoclonal antibodies would be considered not medically necessary. So, you couldn't combine more than one of these monoclonal antibodies. It's prescribed or in consultation with the specialist in allergy, pulmonary, or immunology. So, they don't have to be the allergist. They could be a primary care doctor that is working in an allergy clinic or closely with the pulmonologist or immunologist. We would approve it for 12 months. The reauthorization criteria would really be just documentation of improved or sustained clinical benefit compared to the baseline measure, or stable asthma control. Then, we would then again approve it on an annual basis. Any questions for asthma?

So, moving onto the urticaria, we would approve omalizumab when they have a diagnosis of chronic idiopathic urticaria and documentation that rules out all other causes of urticaria, including all potential triggers. The patient continues to have spontaneous urticarial flares in the absence of potential triggers while on optimal management of underlying condition or the triggers. Documentation of functional impairment due to poor urticaria control or exacerbation. So, interruptions of the activities of daily living, insomnia, missing school or work, and the patient is compliant with an antihistamine at the maximally tolerated dose, unless it's contraindicated. They would not be using omalizumab with one of

the other monoclonal antibodies listed there. The patient is at least 12 years of age. Then again, prescribed in consultation with a specialist in allergy, pulmonology, or immunology. There would be clinical documentation of improved or sustained clinical benefit from reduced urticaria symptoms, such as reduced missed days from work or school or insomnia due to itching. You'll notice I don't think we made changes to this one. That's the reauthorization criteria for urticaria. Any questions or concerns about that? Any changes?

Lisa Chew: I'm trying to tie in what happened earlier today. So, at the P&T, we just passed a motion for that class of drugs to be only applicable for asthma, not urticaria. So, how does this affect this policy here?

Donna Sullivan: So, that particular class for the P&T was really for the preferred status of the drugs on the Washington PDL. So, now, what we're doing is looking at the drugs for the PA policy for Medicaid. So, even though you decided that class was only for asthma, we still have to cover Xolair for its FDA labeled indications. So, we do need to consider coverage for the urticaria.

Christopher Chen: Just a quick question on this last bullet. Are people with chronic idiopathic urticaria consistently treated by a specialist in allergy or immunology or are dermatologists usually the one are kind of primarily managing this?

Donna Sullivan: Good question. We can definitely add dermatology to this list. Okay.

Lisa Chew: So, Donna, do you want to go through and approve each policy one by one or do them all and approve?

Donna Sullivan: So, what we'll need to do is, we'll have to go back to each of the drug classes that we looked at earlier today. The motions you made for the Washington PDL are really specific to the Washington PDL. So, we didn't include our tried and failed two, and our recommendations like we typically do for the Medicaid formulary or preferred drug list. So, we were gonna go back and do motions for the PCSK9 inhibitors, ADHD, the biologics class, and the atopic dermatitis class. So, we can, I was thinking about reviewing the policy and then going back and making the drug class

motion for that. Or we can do them individually. Really, it's up to you, which you feel is more efficient.

Lisa Chew: I don't have a preference. It sounds like the first option would maybe be more efficient.

Donna Sullivan: Okay. Yeah. Sure, um, so are there any other changes or suggestions for the policy? I'm not sure. Was there any stakeholder input on the policy?

Lisa Chew: No stakeholder input.

Donna Sullivan: Okay.

Christopher Chen: Were there other references besides the manufacturer? Is there [inaudible]?

Donna Sullivan: At this point in time, no.

Christopher Chen: Oh, okay.

Donna Sullivan: I am going to skip to the motion and make a few changes. Maybe we should do the other Dupixent also first. 'Cuz, I think that they're both included in this particular class, or the other, let's do the other antimonoclonal antibody policy first. Then, we'll come back to the motion. Sorry. Okay. So, the next antiasthmatic monoclonal antibodies is the IL-5 antagonist. So, we're looking at Nucala. So, essentially, we're saying Nucala is medically necessary when it's used as an add-on maintenance treatment with severe asthma with eosinophilic phenotype. It's used for the treatment of eosinophilic granulomatosis with polyangiitis in adult patients. Other drugs in this class include Fasenra and Cinqair. They may be considered medically necessary when used in add-on maintenance treatment with severe asthma with eosinophilic phenotype.

So, the specific criteria for the drugs, we're looking for documentation of blood, eosinophil count in absence of other potential causes of eosinophilia with one of the following: Either greater than or equal to 150 cells/mL in the prior six weeks or greater than or equal to 300

cells/ml in the prior 12 month period. They must have controlled or inadequately controlled severe asthma defined by an FEV less than 80% predicted, or two or more bursts of systemic corticosteroids in the previous year. Also, frequent, at least twice per year, additional medical treatment, such as ED visits similar to the other policy, poor symptom control with an ACQ score consistent greater than 1.5 or ACT score less than 20. The history of failure, remains symptomatic after six weeks. There is contraindication or intolerance to the high dose. Inhaled corticosteroids in combination with additional controllers. It does need to be used in combination with the additional controller medications combination therapy with the monoclonal antibodies. Other monoclonal antibodies will be considered not medically necessary. There are age limits for the particular medications. So, the mepolizumab the patient needs to be 6 years or older. Benralizumab greater than 12 years. The raslizumab greater than or equal to 18 years. If those criteria are met, we will approve it for 12 months. Then reauthorization criteria, again, is just documentation of disease improvement compared to baseline. Then, it would be approved for an additional 12 months.

The next indication, the EGPA, documentation of the eosinophil count, same as above. Also, white blood present outside the blood vessels, or migratory spots or lesions on a chest x-ray showing the pulmonary infiltrates. Or, they have sinus problems, acute or chronic sinusitis, or damage to one or more nerve groups, monotherapy or polyneuropathy. They have documentation that the patient has a history of EGPA for at least six months with a history of relapsing or refractory disease while using maximally tolerated inhaled or oral corticosteroids for 90 days. Treatment with a DMARD, such as azathioprine, cyclophosphamide, or methotrexate in the past 90 days has been ineffective or not tolerated, or all oral DMARD's are contraindicated. It needs to be prescribed in consultation with a specialist in allergy, cardiology, hematology, pulmonology, or rheumatology. The patient must be greater than 12 years of age. Again, combination use with other monoclonal antibodies would be considered not medically necessary. Reauthorization criteria, again, is just documentation of disease stability or improvement compared to baseline, as demonstrated by one of these items listed here. They are not using any other monoclonal antibody. Any questions so far

on this? Okay. Any questions from staff? Comments before we move on? Okay. Now, I think we are ready to move to the motion.

So, our recommendation for the preferred drug list for Apple Health is that all products are considered safe and efficacious and eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of 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, and we need to do... you recommend that we approve, I guess, the prior authorization criteria as edited. I don't know. I am going to grab these policy numbers real quick. Okay. Are you able to read that? Do I need to make it bigger?

Lisa Chew: So, do we make a motion on this slide or...

Donna Sullivan: Yeah. I'm going to...

Lisa Chew: ...Okay.

Donna Sullivan: ...actually have it, I think, on the next slide, but I'm just gonna add something like that if we can. Okay. This will make it bigger.

Virginia Buccola: I move that all products in the asthma and COPD agents' monoclonal antibody drug class are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of the Health Care Authority. All nonpreferred products require a trial of 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. We approve...

Donna Sullivan: Whoops. I'm sorry.

Virginia Buccola: ...the prior authorization criteria policies as stated. These were reviewed and edited.

Donna Sullivan: Alright. I just had to make an edit there on the slide. So, when you say we approve the prior authorization criteria, policies, as stated. No. Okay. Thank you.

Virginia Buccola: Yes.

Nancy Lee: I second that motion.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Motion carries.

Donna Sullivan: So, the next policy that we're going to go over is the atopic dermatitis, specifically Dupixent. That's the wrong one. So, in general, this note at the top is pretty much the same note on all of the policies, just a generalized statement that allows us freedom to include any new indication, as they come out on the market prior to us actually getting the policies updated. If we stop in our update process, as new indications come out, we'll never get any policies finished. So, that's why we made that particular statement at the top. So, for Dupixent, it's an interleukin-4 receptor antagonist used in the treatment of moderate to severe atopic dermatitis when conventional therapy is not effective. It's also indicated for add-on maintenance treatment for moderate to severe asthma with eosinophilic phenotype or oral corticosteroid dependent asthma. So, we consider it to be medically necessary when it's used for treatment of a severe atopic dermatitis when the disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable, as an add-on maintenance therapy to moderate to severe asthma with eosinophilic phenotype, or as an add-on or maintenance treatment for moderate to severe oral corticosteroid dependent asthma, and also as an add-on maintenance treatment of chronic rhinosinusitis with bilateral nasal polyposis or just nasal polyps in patients that are 18 years or older. So, this last bullet is a new indication, since we reviewed the policy last time.

So, the specific approval criteria is first atopic dermatitis is that it's severe chronic atopic dermatitis with a percent of body surface area involvement of at least 10%, or disease severity scale scoring to demonstrate severe chronic atopic dermatitis, such as the investigator's global assessment, IGA, a score of 3 or greater or the eczema area and severity index. Also, clinical documentation of functional impairment due to the atopic dermatitis, such as limitations of activities of daily living, skin infections, or sleep disturbances with a history of failure defined as unable to achieve or maintain remission of low or mild disease intolerance to contraindication or clinically appropriate to the following medications. So, two topical corticosteroids for daily treatment for at least 14 days each. So, kids and adolescents, children and adolescents, failure of two medium-potency corticosteroids in the last six months, unless member has contraindications to all preferred topical steroids in the medium potency class. For adults, failure of two high or very high potency corticosteroids in the previous six months, unless there are contraindications to those preferred products. We also, in addition to those corticosteroids, require use of one topical calcineurin agent, so either pimecrolimus or tacrolimus. We are recommending that this gets removed, I believe. Is this... no? Okay. This was the other policy? Okay. Never mind. There was some discussion earlier. So, we also required one of the following, either phototherapy, or we try one of the following systemic immunosuppressants. So, methotrexate, cyclosporine, azathioprine, or mycophenolate be tried before we allow the Dupixent for atopic dermatitis. Also, the patient needs to be older than 12 and we're asking that it be prescribed in consultation with a specialist in dermatology, allergy, or pulmonology. Any questions or suggested edits?

David Johnson: Is there a reason why we have pulmonology on the list for atopic dermatitis?

Donna Sullivan: My guess is that we just copied and pasted it from the asthma. I don't know, probably not. So, we can delete that unless there is any, okay. Okay. And we would approve it for six months at first. Reauthorization criteria essentially is that disease stability or improvement defined by reduction in body surface area involvement of at least 20% achieved or maintained clear or minimal disease from baseline; experience or maintenance to decrease in eczema area and severity index;

improvement in functional impairment, which may include improvement in limitation of ADL's; reduced skin infections; reduced instances of sleep disturbances. If that is met, then we will approve it for a year after that first initial six months. Any questions before I move on?

Christopher Chen: Do we want to specify the number of sessions of phototherapy that should be tried before approval?

David Johnson: That's not... any of the other policies that have that don't specify that. We just leave that at, if they say they've tried and failed it, we leave that up to the discretion of the provider. Of course, 99% of all the providers claim a reason why they can't do it anyway. So, it's rarely, if ever, used.

Donna Sullivan: Would you have a recommendation of how many sessions?

Christopher Chen: I haven't personally treated this myself, but from what I understand, benefit isn't typically seen until after at least ten treatments.

Donna Sullivan: Makes sense, I guess. We could add it. Or we could just use that as a kind of in the back pocket. Any comments from the committee?

Jordan Storhaug: I think that is kind for noneffectiveness, but they could have a reaction to getting phototherapy. And then, you wouldn't want to have them go through ten of them. So, I guess I suggest, it's probably okay to leave it just as it is.

Donna Sullivan: Okay. Any other comments before we move onto the next indication? So, the asthma with eosinophilic phenotype documentation of the blood eosinophil count and one of the following: So, greater than or equal to 150/mL in the prior six weeks or 300 cells/mL in the prior 12 months; uncontrolled asthma, as defined by an FEV less than 80%; two or more bursts of systemic corticosteroid in the previous 12 months; poor symptom control; frequent additional medical treatment, such as the ED or treatment with oral corticosteroid, emergency department visits, etc. that are listed there; history of failure remains, meaning that they are still symptomatic after six weeks of treatment; or they have a contraindication or intolerance to the high dose inhaled corticosteroids and other controller medications. It needs to be used in combination

with other controller medications, but not in combination with any other monoclonal antibody. The patients are required to be 12 years of age or older. Prescribed in consultation with a specialist in allergy, pulmonology, or immunology. Again, initial six-month approval with reauthorization criteria if they are met, which is documentation of improvement compared to baseline, we'll approve it for a year after that.

Pretty much, the next for the asthma with oral corticosteroid dependence, the criteria are essentially the same for the severity of asthma, as listed here. They have to have the diagnosis of asthma and the oral corticosteroid therapy dependent. They have remained symptomatic after six weeks of treatment on those steroids. They are also using the other controllers. Again, not to be used in combination with other monoclonal antibodies. This is add-on therapy. So, they need to remain on their controller medications. Patients need to be 12 years of age. It needs to be prescribed in consultation with a specialist in allergy, pulmonology, or immunology. Again, initial six-month approval. Upon reauthorization, documenting clinical benefit, we would then approve it for a 12-month period.

Then, for the nasal polyp diagnosis, it may be approved when all of the following criteria are met, clinical documentation of the chronic rhinosinusitis with bilateral polyposis; history of persistent symptoms of rhinosinusitis after completion of two months of intranasal corticosteroid use; continued use of intranasal corticosteroids while using dupilumab is required; history or failure, intolerance or contraindication to short courses of systemic corticosteroids either oral or injectable; prescribed in consultation with an ear, nose, and throat specialist or allergy specialist; patient is 18 years of age or older. So, it would be approved initially for six months. Then, reauthorization criteria documenting clinical benefit would be approved for 12 months after that. The rest of this is really just summarizing the indications and the dose and quantity limits for Dupixent. So, I think we are ready to go to the motion. Okay. So, our recommendation is pretty much our standard recommendation. All products are safe and efficacious and are eligible to be preferred and grandfathered at the discretion of the Health Care Authority, and we require a trial of two preferred products before a nonpreferred product would be preferred unless there are contraindications or a clinical reason

why a patient cannot take the preferred drugs, and of course, if there's only preferred product, they would only need to try the one preferred product, and then approve the prior authorization criteria, as we just reviewed and edited in the policy 90.27.30.20. That's our recommendation. Okay. Then, here is the motion. Any suggested changes to the motion?

Lisa Chew: I move that all products in the dermatologics atopic dermatitis drug class are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of 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. We approve prior authorization criteria, as reviewed and edited in policy 90.27.30.20.

Diane Schwilke: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Okay. The motion carries.

Donna Sullivan: Okay. So, the next policy that we're looking at is the atopic dermatitis Eucrisa. We probably should have added this one to that motion we just made. Sorry. Which one is it in? I think it's... Okay. So, Eucrisa is a topical phosphodiesterase 4 inhibitor. It is indicated for the treatment of atopic dermatitis in patients 2 years of age and older. So, we consider it for treatment with that indication. Our specific criteria for using Eucrisa is that the patient must be 2 years of age or older; have a diagnosis of atopic dermatitis with documentation of baseline evaluation of the disease including severity of the symptoms. Dave correct me, did we remove these tests from this? That was the recommendation? We recommend not specifying which test to use, mostly because if we have multiple prescribers using different tests, then it becomes challenging. So, we're recommending that we remove that list of tests. We also have a history of failure to the daily use of all of the following: Tried a least

two topical steroids, corticosteroid, medium or higher potency for at least 14 days in the previous six months, unless contraindicated to the preferred topical corticosteroids. Contraindications would include treatment of sensitive area, such as the face, anogenital area, or skin folds; steroid induced atrophy or longterm interrupted use of steroids; trial at least one calcineurin inhibitor for at least 28 days unless contraindicated.

David Johnson: You can append 3. We took out C. So, you just take, where it says all A, B, and C, just take out the C.

Donna Sullivan: Here?

David Johnson: Yeah.

Donna Sullivan: Okay. Reauthorization criteria is clinical documentation of disease stability, or improvement from baseline. Then, it would be approved. Initial approval would be for six months. Then, upon documentation of improvement, we would approve for 12 months after that. Any questions? Okay. So, my recommendation is, we go back and amend the motion.

Jordan Storhaug: The next topic looks like isn't it atopic dermatitis.

Donna Sullivan: It is? Okay. We'll keep going then. Let me put this one here in the motion. That's the same number. Okay. We will fix this. I think I just grabbed it out of the wrong policy. Okay. So, the next one, atopic dermatitis. So, the topical immunosuppressives. So, this is for the medications Elidel and Protopic. They are indicated for second line topical treatment of atopic dermatitis in patients 2 years of age and older. Pimecrolimus right now is our preferred agent. Either one of them will be approved when all of the following is met: The patient is 2 years or older; has diagnosis of atopic dermatitis with a baseline evaluation including severity. They have tried at least two topical corticosteroids of medium or higher use for at least 14 days. We've already read through this. It's essentially the same as the previous policy. The patient may not have any of the following: Immunocompromised status; severely impaired skin barrier; risk presence of malignancy, skin or lymphoma.

There are dose limitations, except for when written by a dermatologist. So, pimecrolimus and tacrolimus 0.03% greater than or equal to greater than 2 years of age, or the tacrolimus 0.1% when they are at least 16 years of age or older. The initial criteria would be approved for six months. Reauthorization criteria documentation of disease stability or improvement. Then it would be authorized for 12 months. Any questions?

Lisa Chew: The Eucrisa, the policy that we reviewed before in the reauthorization criteria had all those indexes for reauthorization. That was taken out. Yeah. Okay.

Donna Sullivan: So, this is correct then? We took it out. I'm sorry. I apologize. I forgot to mention that. We had taken it out of the one policy. And we had failed to remove it from all the other policies. So, yes. Those criteria are taken out. What we're viewing on the screen is what we're actually approving.

David Johnson: Could you go back to the calcineurin policy? Down at the bottom on the dose limits, I think there is one correction there. Scroll down just a tad more. Okay. It's been fixed. It used to say 15, which isn't available. So, Okay. Thanks.

Donna Sullivan: So, I think now we're... that was the last policy. So, there is no ADHD policy. So, that will be stricken from the agenda. So, we're ready to go back to the dermatology one.

Constance Huynh: I was just gonna ask... I thought that maybe we need to actually amend the motion?

Donna Sullivan: Correct.

Constance Huynh: Okay. Do you want me, I can do it. I didn't know if you had anything else to say?

Donna Sullivan: No.

Constance Huynh: Okay. All right. I move that we amend the previous motion made by Dr. Chew to add the policy's 90.23.00 and 90.78.40.

Virginia Buccola: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? The motion carries. Okay. I think we move onto the opioid policy updates.

Donna Sullivan: So, looking at time, so we are ten minutes behind schedule. So, what I would recommend is maybe we skip the opioid policy update and come back to it, if we have time at the end, since there's just information only. I don't need a decision from you today. So, with that, we would move to the COPD agents. Thank you.

Lisa Chew: We have one stakeholder, Piao Ching. He's going to make some comments. Please state your mail, who you represent, and you will have three minutes.

Piao Ching: Hi. Good afternoon. My name is Piao Ching. I'm with Pfizer medical outcome specialist. I am here to provide medical information on Eucrisa, in support of Pfizer's request to reconsider the step that is one Eucrisa. As Donna mentioned earlier, Eucrisa is a phosphodiesterase-4 inhibitor indicated for topical treatment of mild to moderate atopic dermatitis, or AD, in patients 2 years of age and older. This is the only FDA approved topical PDE-4 inhibitor, and the first novo topical prescription medication approved for AD in more than a decade. Eucrisa can be applied twice daily to the skin anywhere on the face and body. The product is for external use only and is not for [inaudible], oral, or intravaginal use. The safety and efficacy for Eucrisa was established in two double-blind randomized [inaudible] control studies. At baseline, 38.5% of the subjects had an investigator static global assessment, or ISGA score of 2, which is mild, and 61.5% had an ISGA score of 3, which is moderate, in the overall assessment of AD on a severity scale of 0 to 4. In both trials, subjects were randomized 2:1 to receive Eucrisa or a [inaudible] applied twice daily for 28 days. The primary efficacy endpoint was the proportion of subjects at day 29 who achieved success, defined as an ISGA grade of

clear, which is a score of 0, or almost clear, which is a score of 1 with a 2 or greater improvement from baseline. In trial one, 32.8% of Eucrisa met the primary efficacy endpoint versus the 25.4 on [inaudible]. In trial two, 31.4% on Eucrisa met the primary efficacy endpoint versus 18% on a [inaudible]. Safety assessment included adverse events, vital signs, ECG, and clinical [inaudible] values. The most common adverse effect occurring in greater than 1% of subjects was application site pain, 4% in the treatment group versus 1% in the behavioral group. Study discontinuation rates, due to adverse events, were the same for Eucrisa and [inaudible] at 1.2% for both groups. Additionally, Eucrisa was studied in a 48-week open label safety extension study. No safety signals were identified from vital signs or lab assessment. There were no reports of longterm cutaneous adverse reaction during extended use of Eucrisa. The majority of the treatment adverse events were considered mild to moderate in severity with 93% of treatment related adverse events considered unrelated to treatment. In conclusion, I would like to thank the committee for listening to my testimony. Again, I would ask you to reconsider the current step edit on Eucrisa. Specifically, on stepping through the TCI in order to obtain Eucrisa that will limit the options available for Medicaid patients. I would be happy to respond to any questions you may have.

Lisa Chew: Thank you, very much. Any questions from the committee? Okay. Thank you. All right. Shall we move onto asthma and COPD agents? Okay.

Umang Patel: So, the next, we'll look at COPD agents. Similar to, as I mentioned with the GINA guidelines earlier for asthma, over the next three topics, there will be some overlap between asthma and COPD. I will go over the guidelines during this treatment class, but moving forward, it'll be in your slide set, but we'll skip right over that.

To go over the overview, COPD, or chronic obstructive pulmonary disease, is a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema. The airflow obstructions are generally progressive and may be accompanied by airway hyperreactivity and may be partially reversible. This progressive, persistent obstruction or limitation of airflow, which is associated with an enhanced chronic inflammatory response in both the airways and the

lungs to noxious particles or gasses. Although the precise distinction between chronic bronchitis and emphysema are a subject of debate, common beliefs hold that chronic bronchitis is responsible for roughly 85% of COPD. Patients with chronic bronchitis experience intermittent airway inflammation and excessive mucus production that leads to frequent, prolonged episodes of productive cough. In contrast, 15% of patients with COPD suffer primarily from emphysema, in which destruction of infrastructure of alveoli and distal airspaces that provide gas exchange and elastic recoil occurs. Both chronic bronchitis and emphysema predispose patients to a common collection of symptoms and impairments in respiratory function, such as reductions in forest expiratory volume in one second or FEV-1, forced vital capacity, or FVC, FEV-1/FVC ratio and forced respiratory flow. Exacerbations and comorbidities contribute to overall severity in individual patients. COPD continues to be a leading cause of chronic morbidity and mortality worldwide carrying with it significant economic and social burden. It's projected by WHO to become the third-leading cause of death by 2030. In their 2017 National Health Interview Survey, the CDC reported that the percentage of adults who are diagnosed with chronic bronchitis in the past year was 3.5%, and those that have ever been diagnosed with emphysema was 1.4. However, the U.S. Preventative Taskforce recommends against routine screening in asymptomatic adults.

Continuing on to the next slide. You'll see the indications, and this is stratified by the mechanism of action. Over the next two slides, we have three classes broken down into COPD. We have antimuscarinics short-acting, which would be ipratropium inhalation solution, Atrovent HFA. Then, we have antimuscarinics longacting, which are Turdorza Pressair, Lonhala Magnair, Seebri Neohaler, Yupelri, Spiriva Handihaler, Spiriva Respimat, and Incruse Ellipta. Then, we have the beta-2 agonists/antimuscarinic combos, short-acting where you see have albuterol, ipratropium inhalation solution and we have Combivent Respimat, as well.

Then, on the next slide here, continuing with the indications, we have beta-2 agonists longacting antimuscarinic combinations composed of Bevespi Aerosphere, apologize for my pronunciation, Utibron Neohaler, Stiolto Respimat, and Anoro Ellipta. Lastly, a PDE-4 inhibitor, Daliresp.

Continuing on with the dosing and availability, in terms of, I'll keep the dosing and availability slide in front of you, just to give you a little bit of information about the classes itself, all longacting beta agonists, LABAs, were previously contraindicated and carried a box warning in patients with asthma without use of a longterm asthma control medication due to the risk of asthma related death. I understand we're talking about COPD, but I felt remiss if I didn't mention the blackbox warning. In December 2017, the FDA released a communication based on four large clinical safety trials and determined treatment of asthma with a LABA in combination with an ICS does not lead to significantly more serious asthma-related adverse events than treatment with an ICS alone. As a result, the box warning regarding asthma-related deaths was removed from ICS and LABA labeling. The box warning regarding increased risk of asthma-related death with the use of LABAs alone to treat asthma will remain in labels for single component LABAs. There are some drug interactions, particular monoamine oxidase inhibitors and TCAs, tricyclic antidepressants should be used cautiously with albuterol containing products due to potentiation of cardiovascular effects. A two-week discontinuation period for MAOIs and TCAs is suggested prior to initiating therapy with any albuterol-containing products.

We have the final three subclasses. In terms of pediatrics, so COPD, keep in mind, is a disease that does not normally occur in children. So, safety and efficacy of Atrovent, albuterol, ipratropium inhalation solution, Combivent Respimat, Bevespi Aerosphere, Lonhala Magnair, Seebri Neohaler, Utibron Neohaler, Daliresp, Turdorza Pressair, Yupelri, Spiriva, and Anoro Ellipta in pediatric patients have not been established. The efficacy of tiotropium inhalation spray, or Spiriva Respimat, has not been demonstrated in patients less than 18 years of age with COPD, but efficacy is seen in patients with asthma. In terms of pregnancy, keep in mind, ipratropium is pregnancy category B, as in beta. The remainder of the drugs in this class are either category C, as in Charlie, or have insufficient safety and efficacy data.

To move onto the guidelines here, and these are the GOLD guidelines. Again, I'll go over these this round, and then if we see them in the upcoming TCRs, we'll briefly go over them. So, the GOLD guidelines in

2019, the global initiative for chronic obstructive lung disease stresses that a diagnosis of COPD should be considered in any individual who has dyspnea, chronic cough or sputum production, and a history of exposure to risk factors specific to the disease. Spirometry is required to effectively establish a clinical diagnosis of COPD. The COPD assessment test, or CAT, and the Clinical COPD Questionnaire, CCQ, is recommended for a comprehensive assessment of symptoms, and the Modified Brith Medical Research Council Questionnaire may be used but only assess breathlessness. Prior to 2017, patient groups were categorized into an alphabetic A, B, C, D classification system based on exacerbation risk and symptoms in combination with airway limitation. However, patients are now classified separately by their GOLD severity. For example, airflow limitation from 1 to 4, and exacerbation or symptom assessment, so for example a patient could be GOLD grade 4, group D, as in Delta. The definitions of airflow limitation and numerical values for exacerbation and symptoms has not changed, and they are summarized below in that little box.

Moving onto the next slide here. Continuing on with the GOLD 2019. They recommend treatment plans for COPD based on the aforementioned patient group categories based on disease severity, airflow limitation, symptoms, comorbidities, and exacerbation/hospitalization risk, although, all treatment should be individualized. Bronchodilator medications continue to be central to symptom management of COPD across all groups. For patients in Group A, a short-acting inhaled bronchodilator, a beta-2 agonist or an antimuscarinic used on an as-needed basis is recommended, as the first choice, while a longacting bronchodilator, a beta-2 agonist for antimuscarinic is considered as an alternative. For Group B, as in beta, regular use of a longacting beta agonist, or longacting antimuscarinic is recommended while the combination of a LABA plus a LAMA can be considered an alternative treatment. There is insufficient evidence to recommend one longacting over another. For Group C, as in Charlie, focus on monotherapy with a longacting bronchodilator with preference given to LAMAs. If exacerbation persists, then fixed combinations of LABA/LAMA or LABA-inhaled corticosteroids may be tried, due to increased risk of pneumonia with ICS agents, a LABA/LAMA combination is preferred. Finally, Group D, prescribers may utilize the same initial

therapeutic plan as those in Group C with a goal of reducing exacerbations. Initial therapy with a LAMA is recommended, as it has effects on both breathlessness and exacerbations in patients with a more severe symptom, for example with a CAT score of 20 or more, can be initiated on a LABA/LAMA combo. Prescribers may consider a LABA/ICS combo for patients with blood eosinophil count over 300 cells/mL, as this combination has the greatest likelihood of reducing exacerbations, or maybe preferred in patients with a history of asthma. There is some evidence for use of triple-therapy, ICS with LABA with LAMA, in patients with persistent breathlessness or exercise limitation. If exacerbations still occur with triple therapy, then an oral PDE-4 inhibitor, Daliresp, which is indicated to decrease the frequency of exacerbation or worsening symptoms of severe COPD may be added in patients with an FEV-1 score of less than 50% of predicted and chronic bronchitis. Longterm monotherapy with an ICS at any stage has been shown to be less effective than its use with the combination with LABA. Lastly, following initial therapy, patients should be reassessed for attainment of treatment goals and therapy adjusted, as needed.

On the last slide here, um, the European Respiratory Society, ERS, and American Thoracic Society Joint Guidelines in 2017 recommend LAMA over the use of beta-2 agonist LABA monotherapy to prevent exacerbations in patients with at least one exacerbation during the year. Suggest treatment with roflumilast to prevent future exacerbations in patients who have COPD with severe or very severe airflow obstruction and symptoms of chronic bronchitis and exacerbation despite optimal inhaled therapy, so similar to the GOLD guidelines.

Lisa Chew: We have one stakeholder, Thomas Plucinak. So, please state your name, and you can correct how I said your last name, as well as who you represent and three minutes.

Thomas Plucinak: You get an A, not an A+, but an A. So, thank you for the time. I'm Tom Plucinak, and I'm the GSK respiratory medical science liaison for the Pacific Northwest. Like I said before, supporting our asthma and COPD medications. So, with regards to this section, I wanted to discuss our anticholinergic, or Incruse Ellipta, and our LABA/LAMA combination, LABA anticholinergic combination, Anoro Ellipta. For this, I'd really like to

stress a couple critical points for the committee to consider. Number one is going to be the importance of the inhaler in asthma and COPD treatment. Also, I wanted to say that not all LABAs and LAMAs appear to be the same. So, on the first point, one of the main strengths of these medications, like I said, Incruse and Anoro for the [inaudible] device, is that they're delivered via the Ellipta inhaler. This is important for a number of reasons. Number one, inhaler misuse is rampant, as probably many of you have seen in real life, is rampant in the real world, and technique errors have unsurprisingly been linked to higher rates of major events, such as hospitalizations and ER visits. Accordingly, the most well-known COPD treatment strategy document, the GOLD guidelines, which are very nicely just covered, have begun to stress the importance of inhaler training and device considerations. Number two, because we've done the studies to ask patients, we are able to say that the Ellipta device is 'easy or very easy to use' for the vast majority of COPD patients. Critical errors, which are inhaler technique mistakes that are so bad that patients likely don't receive their prescribed end purchased doses. They're also important to look at. We saw that the number of critical errors made with the Ellipta was significantly lower compared to other prominent inhaler devices, such as the Diskus, the Handihaler, the classic MDI, as well as the Respimat in COPD patients that were unfamiliar with the devices tested. Number three, the last one in this section, a medication delivered by the Ellipta inhaler exists for all but the mildest severities of COPD and asthma, and all these are approved for once daily dosing. This means that as a patient navigates the healthcare system, primary care, hospital, urgent care, specialists, etc., and as their disease burden progresses or diminishes, training and administrative burden for patients and HCP's associated with inhaler switching is minimized. This is an especially important consideration for COPD patients who tend to have significant comorbidities and often complicated overall treatment regimens. A couple more points here. With regards to molecule performance, the second point I mentioned, both of these agents, Incruse, Ellipta, and Anoro Ellipta have been shown to provide greater lung function and improvement compared to prominent active comparators on the preferred medications list, PDL. Specifically, Incruse, or umeclidinium, the generic name, has been shown to provide a 60% greater improvement in lung function and benefit compared to tiotropium or Spiriva in COPD. Also, Anoro has been shown to provide a

41% improvement in lung function improvement compared to tiotropium olodaterol or Stiolto, in the Respimat. Of course, published references for these are available upon request if anyone is interested. So, in summary here, accordingly, due to the simplicity and versatility of the Ellipta delivery system, and because there are data that suggest new patients may do better on these medications compared to some others in this category, GSK requests that these medications be added, as a preferred option for patients to the PDL. Thank you.

Lisa Chew: Any questions? Alright. Thank you, very much.

Leta Evaskus: The way we're going to do this is, we're going to go through all of Umang's presentations, and if there are stakeholders after each subject, then we'll hear them, but we're going to make a motion, we'll wait for the motion to the very end.

Donna Sullivan: I'm going to amend that. So, we're going to go through all of the asthma COPD classes, or the bronchodilators, the next one, two more classes. Then, we'll make a motion on all the asthma-related drugs. Then, we'll go through the dermatologics and then make the motion on the dermatologics.

Umang Patel: Alright. So, we'll be moving right along to the short-acting and longacting beta agonists. I feel like I don't need to give a lot more background on this disease state, but I apologize, I have a few more slides on this. Beta-2 agonist bronchodilators are the medication of choice for the treatment of prevention of bronchospasm associated with asthma, and prophylaxis for exercise-induced bronchospasm, EIB, in adults and children. They are also used in the treatment of chronic COPD. In some patients with chronic asthma, a clear distinction between asthma and COPD may be difficult. Differentiating features between asthma and COPD include the onset of asthma is usually in childhood, whereas COPD could be in midlife. Asthma symptoms vary widely from day to day and are generally worse at night or early mornings, whereas COPD symptoms progress slowly. Allergy, rhinitis, and/or eczema, as well as obesity, are usually present in asthma patients. There may be a genetic link with asthma, whereas COPD is generally due to tobacco smoke and occupational pollutants.

On the next slide here, we have background on asthma. I'm going to skip the top two, because this was presented earlier. So, medications to treat asthma are classified as controllers or relievers. Controllers are medications taken daily on a longterm basis to maintain asthma control. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve symptoms. So, short-acting beta agonists, or SABAs, have a rapid onset of action and are useful for temporary relief of bronchoconstriction and the accompanying acute symptoms, such as wheezing, chest tightness, and cough. They have not been shown to be beneficial, as the longacting controller medications for chronic asthma management. Also, increased used of reliever medication is a warning of deterioration in asthma control, and that indicates a need to reassess the treatment. So, to give a little bit more on the mechanism of action, beta-2 agonists stimulate the adenylyl cyclase, the enzyme which essentially forms cyclic camp in the body, increased cyclic camp is associated with relaxation of the bronchial smooth muscles and inhibition of release of mediators for immediate hypersensitivity of inflammatory cells, and essentially bronchodilates.

Going onto COPD here, pharmacotherapy for COPD is used to decrease symptoms, reduce frequency and severity of exacerbations, hospitalizations, and improve health status and exercise tolerance. Bronchodilator medications are essential to symptomatic management of COPD. It improves emptying of the lungs, tends to reduce dynamic hyperinflation, rest and during exercise, and improve exercise performance. Given either on an as-needed basis for the relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. Regular bronchodilation with these drugs does not modify the decline of function in mild COPD or the prognosis of the disease. The principle bronchodilator treatments are beta-2 agonists, anticholinergics, and theophylline. These may be given as monotherapy or in combination, and while SABAs can be used on an as-needed basis in mild COPD, regular treatment with a longacting agent is required, as the disease progresses.

So on the next slide here, I have broken down the indications and the dosing and availability. First will be SABAs and then we'll go into LABAs

after that. So, for short-acting inhalation agents, we have ProAir RespiClick, ProAir HFA, Proventil HFA, Ventolin HFA; albuterol inhalation solution, low-dose inhalation solution; Xopenex HFA and Xopenex for short-acting inhalation agents. The indications are broken down whether or not they have prevention and treatment for a reversible bronchospasm along with a relief, if they have an additional indication for exercise-induced bronchospasm, COPD, and the, um, pediatric indication is broken down on the far column on the right. Then, we also have oral agents, such as albuterol oral syrup, oral tablets, metaproterenol, oral syrups and tablets, and terbutaline tablets, as well.

Moving onto the next slide here. We have short-acting inhalation agents, as well. So, we have... while this slide is up, I will give more information about these medications. I mentioned this earlier but with drug interactions, be careful with MAOIs and TCAs again. There can be a drug-drug interaction. A 14-day kind of washout period is recommended. Beta-blockers are... there is a drug interaction with beta-blockers, as one can imagine. They not only block the pulmonary effect of beta agonist but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not be treated with beta-blockers; however, under certain circumstances, such as prevention of MIs, there may be no acceptable alternative to the use of beta adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution. In terms of patients who are pregnant, there are no adequate and well-controlled studies of the majority of these agents in pregnant women. Keep in mind, terbutaline is pregnancy Category B, as in beta. All the SABAs excluding levalbuterol concentrate, are pregnancy Category C.

Moving forward to the dosing of the oral short-acting beta agonists. There is no dosage adjustment needed in hepatically impaired patients who use albuterol, albuterol HFA, or levalbuterol, just an FYI. Exercise caution, monitor in patients with renal impairment who use those three, albuterol, HFA, and levalbuterol, as well.

Moving forward to the LABAs, so we have Brovana, Perforomist, Arcapta Neohaler, Striverdi Respimat, and Serevent Diskus. Again, for their

respective indications for prevention and treatment of reversible bronchospasm, exercise-induced bronchospasm, COPD, and the pediatric age indication.

Moving on to the dosing and available while we're on this slide. For pediatrics, obviously, Serevent has been indicated for the prevention and treatment of asthma and EIB in children as young as 4 years of age, but the safety and efficacy for the remaining, Arcapta, Brovana, Perforomist, and Striverdi, have not been established in children. In terms of pregnancy, note that Arcapta is pregnancy Category C. The labeling of the remainder are too limited to inform a drug-associated risk of adverse developmental outcomes.

Going on to the next slide here. We have the GINA guidelines. We reviewed this previously. I'm going to ask Leta if you can go to two slides after this to the columns.

So, again, we've gone over the GINA guidelines before, but just to kind of point out where the SABAs and LABAs are indicated based on the GINA guidelines. In terms of other controller options, we have low-dose ICS when SABA is taken. This is an unlabeled indication for step one, and step two, as well. For step one, in ages 6 to 11 and greater than 12. For step two, a leukotriene modifier or low-dose ICS is recommended when SABA is taken. For step three, low-dose ICS and LABA is recommended as a combo for preferred controller.

Moving forward to the next slide, step four, similar to step three, medium dose ICS and LABA are recommended for the preferred controller with high dose ICS and LABA recommended as an alternative controller option in pediatric patients. Lastly, for step five, which is the most severe, high dose ICS or LABA is recommended for preferred controller in patients 12 years of age or older.

Going on to the next slide here. For reliever options, as you can see, as needed SABA is recommended as another alternative reliever option in patients greater than 12 years of age, and is the preferred reliever for patients 6 to 11 years of age for step one through five.

Our final slide for this, the NAEPP, I mentioned this earlier, but they emphasize the importance of asthma control and identified asthma severity as the intrinsic intensity of the disease process. The EPR-3 advises the need to first assess severity, as the basis of initial therapy. Then, assess control to adjust that therapy, based on the stepwise approach. SABA recommends that inhaled short-acting beta agonists are the drug of choice for treating acute asthma symptoms and exacerbations, and for preventing EIB. Regularly scheduled daily chronic use of SABA is not recommended. Use of short-acting agent greater than two days per week for symptom relief is an indication of inadequate asthma control and the need for a step up treatment. The inhaled route is the preferred use due to faster onset of action, fewer adverse effects, and an increased efficacy. Lastly, agents less selective for beta-2 receptor, including metaproterenol, are not recommended, due to excessive cardiac stimulation.

Lisa Chew: Thank you, Umang. Any questions on this section before he moves onto the COPD of the inhaled corticosteroids?

Donna Sullivan: Are there any stakeholders?

Lisa Chew: No. There's no stakeholders. There are stakeholders after the, there is a stakeholder for the inhaled corticosteroids.

Umang Patel: There is no background on this one. I think you guys have probably had enough of that. So, going right into the indications. We will have the glucocorticoids here. Again, the drugs, whether or a generic formulation is available, and the indications are listed above. To give an idea of the mechanism of action, corticosteroid suppress the cytokine generation, recruitment of airway eosinophils and release of inflammatory mediators. These agents thereby block late-phase reactions to allergens, reduce airway responsiveness, and inhibit inflammatory cell migration and activation. Because systemic corticosteroids have a high incidence of adverse reactions, inhaled corticosteroids are preferred for asthma. The longacting beta agonists, LABAs, formoterol, vilanterol, and salmeterol selectively bind to beta-2 receptor in the bronchial smooth muscle, leading to bronchial relaxation and decrease in the release of mediators

of immediate hypersensitivity. The reason I mention longacting beta agonist is, we will also have combination products in this review, as well.

So, going onto the next slide here, you see we have glucocorticoid longacting beta agonists Symbicort, Breo Ellipta, Advair HFA, Advair Diskus, AirDuo RespiClick, and Dulera. Then, we also have a glucocorticoid longacting anticholinergic, longacting beta-2 agonist combination, Trelegy Ellipta.

Okay. Moving on to dosing and availability, again, the dosing similarly to the previous classes has been stratified based on adults and pediatric, and I have listed both initial and maximum, along with the availability.

Moving on here, we also have Alvesco, Aerospan, and Arnuity Ellipta. In terms of... so, special populations. So, for pregnancy, Alvesco is assigned pregnancy Category C, and budesonide is pregnancy Category B, as in beta. Qvar Redihaler, Aerospan HFA, Arnuity Ellipta, Trelegy Ellipta, essentially, the remaining medications in this are not assigned a pregnancy category based on updated or new prescribing information complying with the PLLR rule. There are no adequate randomized clinical trials of beclomethasone dipropionate, budesonide formoterol, flunisolide, fluticasone, or fluticasone combo products, thus a risk versus benefit assessment should be conducted prior to the use of these agents in pregnant women.

Continuing to move forward, here we have additional dosing and availability for Flovent HFA, ArmonAir RespiClick and Flovent Diskus. In terms of, again, continuing special populations for hepatic impairment, close monitoring of patients with fluticasone proprionate and salmeterol, so Advair Diskus, HFA, and AirDuo RespiClick, who have hepatic impairment is recommended due to accumulation of both active ingredients.

We have about three slides left with the dosage and availability. Here, we have Asmanex HFA, Twisthaler, and Symbicort, again stratified. There isn't primarily too much difference. If there is a key difference in one of the medications over the other, I would point it out for you, but essentially, the majority of these are pediatric and adult dosed.

On the second to last slide here, we have Breo Ellipta, Advair HFA, and Advair Diskus. The last one being AirDuo RespiClick, Dulera, and Trelegy Ellipta. Again, there won't be any guidelines on this, because we've gone through the GINA and the GOLD guidelines already.

Lisa Chew: Thanks, Umang. Any questions? So, we have one stakeholder, Thomas Plucinak. You will have three minutes for comments.

Thomas Plucinak: So, hello again, everyone for the last time today. Again, Tom Plucinak, GSK respiratory medical science liaison for the Pacific Northwest. So, the ICS containing medication I really want to talk about, um, is Trelegy Ellipta, which contains anticholinergic LAMA or LABA and an ICS all delivered simultaneously with one inhalation a day via the Ellipta inhaler that I talked about in the last session. So, above and beyond what was already very nicely presented, I'd like to stress the following points for your consideration. So, first off, I'd like to briefly reiterate just what I mentioned about the Ellipta device and device considerations. Number two, the importance of exacerbations and hospitalizations in COPD. Number three, I wanted to make the point that triple therapy is not therapeutically interchangeable with ICS LABAs and most of the things in this category. It should be considered its own category, and this medication is the only single inhaler triple therapy for COPD. So, on the first point, as already noted, one important feature of this medication is that it's delivered via the Ellipta device, like most other COPD asthma medications that we have. I discussed the importance of inhaler errors and discussed our lower inhaler technique errors relative to other available devices in the last section. I'd be happy to reiterate that if anybody has questions. The next point is a very important one, is the importance of exacerbations in COPD. So, exacerbations are a major feature of COPD, and it's important to note that many COPD patients are more exacerbation prone than others. The subset of these are also frequently hospitalized, and unsurprisingly, suffer from worse outcomes and account for a significant proportion of total COPD healthcare and Medicaid expenditures. Accordingly, it is obviously desirable to reduce the COPD exacerbations and hospitalizations. So, the next section, Trelegy is not therapeutically interchangeable with ICS LABA or LABA/LAMA. We saw recently from a large 10,000 patient COPD

exacerbation RCT study, it was actually published in New England Journal of Medicine, 2018, that triple therapy, or ICS LABA plus anticholinergic significantly improved outcomes compared to ICS LABA and LABA/LAMA. Specifically, exacerbations were significantly reduced and hospitalizations were reduced compared to these components, and lung function and quality of life measures were increased compared to ICS LABA and LABA/LAMA. Due to data such as this, the GOLD guidelines recognized triple therapy, as a therapeutically distinct class from ICS LABAs and recommend escalating triple therapy from other COPD maintenance medications, if exacerbations remain uncontrolled, for example. A couple more points, currently if ACPs decide a patient needs triple therapy, the current PDL necessitates patients receive anticholinergic or LAMA plus and ICS LABA and two separate devices with different mechanisms with different dosing frequencies and two different acquisition costs. They would need to fail these treatments to have access to Trelegy or triple therapy dose once a day, all in one device. To finish up here, GSK requests that the committee consider making triple therapy a new or subcategory of medications due to significant proven and GOLD guidelines recognized differences and outcomes compared to ICS LABA, specifically. Furthermore, the current requirement for a double step edit to access Trelegy, the only single inhaler triple therapy, produces an undue barrier to access for Medicaid patients. Thank you, very much. I'm happy to take any questions.

Lisa Chew: Thank you, Thomas. Any questions? Okay. Thank you.

Donna Sullivan: So, before we go to the motions, I want to show you which drugs are actually preferred in these particular classes. Just so you know, the spreadsheet that you have on the... the big spreadsheet, that's... those are the drug classes that are going live October 1st, or went live October 1st. I just wanted to show it to you. If you have any questions, you can submit them to us via email, and we'll be looking at this particular class up here on the screen. So, mostly, I'm just showing right now the preferred drug for anticholinergics. It's typically the generic products; however, Atrovent HFA does have rebates that make it cheaper, as well as Combivent. For the longacting beta agonist, Serevent is our preferred product. We have the generic oral product preferred. ProAir, Proventil, Symbicort, or ProAir and Proventil are our preferred branded albuterol

inhaled agents. Symbicort and Advair and the generic for Advair are our combination, ICS combination products that are preferred, as well as Dulera is also preferred. Then, the single inhaled corticosteroids, we have the generic budesonide, Pulmicort, Flovent Diskus, and Flovent HFA preferred. We also have Stiolto Respimat as the LAMA/LABA combination, Spiriva Handihaler as our longacting muscarinic agent. Then, the monoclonal antibodies, [inaudible] Nucala, Xolair, Cinqair, and phosphodiesterase inhibitor Daliresp. Those are all preferred. So, I just wanted to show you. This is the current state. So, like with the other drug classes, we will consult with Magellan and look to see if there is any opportunity for adding other products, changing these products, and we will do that based on the recommendation that you give us in the motion. So, with that said, let's move to the motion. So, we're talking about... these are the particular drug classes that we have on our PDL, the anticholinergics, the short-acting beta agonist inhaled separate from the oral products, the longacting beta agonist inhaled corticosteroids and combinations, longacting muscarinic agents and their combinations, and phosphodiesterase inhibitors. Our recommendation is that our standard recommendation that they are all safe and considered efficacious. They are eligible for preferred status and grandfathering at the discretion of Health Care Authority. They require trial of two preferred products before the nonpreferred product would be authorized, unless contraindicated or not clinically appropriate, or only one product is preferred. With that, we come to the motion. Is there any edits that you want to make to the motion based on the stakeholder input or the presentation that we had earlier?

Constance Huynh: I actually have a quick question about the standard of two preferred products trial of a drug of the same medication before going to, going to a nonpreferred drug. Is there a reason for that? Is that just the standard for healthcare?

Donna Sullivan: That's the standard that you guys recommended previously, depending on the drug class. Typically, we might have... I think previously, we had said all preferred products, and the committee recommended that might be, sometimes that might be five, six, ten, depending on the class. They recommended that the standard be two.

Constance Huynh: The reason I'm asking is just because of barriers to compliance, as well as for treatment of asthma in some of my patients, and money is an issue and having to go through several different options before reaching the nonpreferred that ends up usually being a little bit more efficacious. So, that's why I'm just asking about the two.

Donna Sullivan: So, with our Medicaid clients, they don't have any copays. So, there's not really an out of pocket difference for them at all. So, I don't know. There is difference in cost in these medications. Typically, that's why when they're determined to be safe and efficacious by the committee that we will look to see which ones will be preferred based on the cost. If you want us to have more than one preferred drug, you can give us, like, a number, if there is any type of device of dosage form, the committee will typically tell us that we have to have, like, an oral form or an injectable form, for example, or a pediatric indication, those types of recommendations. So, that's all the things that you can add to the motion. We just do this to try to be a little bit more expedient. You're able to add or delete whatever you would like, or change.

Jordan Storhaug: I just think the monoclonal antibody part up there, I don't think that applies.

Donna Sullivan: I think that I'm in maybe the wrong one. Hang on. You're right. This needs to go away.

Jordan Storhaug: Then, I'm not sure if it's actually slide 12, I think maybe slide 18 is what you need to refer to?

Donna Sullivan: Thank you.

Jordan Storhaug: And then, I mean, I think I kinda only half think about bringing it up, but I think that we probably do want to have something where we have to have some preferred from each of the listed categories. I think as the verbiage is right now, we could always essentially... we could just have, you know, short-acting beta agonist would be the only thing on preferred.

Donna Sullivan: Do you want to put in a number, or?

Jordan Storhaug: Two is the number that comes to mind.

Donna Sullivan: And this will be, assuming that there is two products in the category. Right?

Virginia Buccola: I move that all products in the asthma and COPD agents' drug classes listed on slide 19 are considered safe and efficacious, and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. Each drug class listed must have at least two preferred agents when possible. All nonpreferred products require a trial of 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.

Nancy Lee: I second that motion.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. Okay. So, it looks like we'll move... well, we were scheduled for a break. Should we take a break? Or should we plug on? Plug on? Five-minute break? Okay. Okay. We'll do a five-minute break.

We're going to go ahead and get things started again. So, we will have Umang do all the dermatology presentations. There are no stakeholders for the rest of the topics.

Umang Patel: Okay. Next will be antipsoriatics. First will be oral, then topical. So, psoriasis, common chronic inflammatory multisystem condition with predominantly skin and joint arthritis manifestations. It is characterized by erythematous plaques and plaques with silvery scales, which negatively impacts the quality of life. It is estimated that over 8 million people in the United States have psoriasis. The prevalence is 1.9% in African-Americans, about 1% of Hispanics, and 3.6% in Caucasians. It usually presents between the ages of 15 to 35 years, but psoriasis can

develop at any age. There are five types. There's plaque, guttate, inverse, pustular, and erythrodermic. Most common type is plaque psoriasis, or psoriasis vulgaris, in which patches or lesions of skin become inflamed and is covered by a silvery white scale. The plaques frequently occur on the skin of the elbows and knees but can affect any area, including the scalp. For patients who have mild to moderate psoriasis, it's generally treated with topical agents. Phototherapy is used when the disease is widespread or unresponsive to topical agents. Systemic agents, including biologic drugs, are usually reserved for patients with moderate to severe disease or those with psoriatic arthritis. For moderate to severe psoriasis, it's defined as involvement of more than 5 to 10% of the body surface area, or involvement of the face, palm, or sole, or disease that is otherwise disabling. Patients with moderate to severe disease are generally candidates for systemic therapy. Options for systemic therapy include methotrexate, cyclosporine, retinoids, biologics, and methoxsalen, or UVA radiation.

Going on to the next slide here, we have the antipsoriatic oral indications. Sorry. One second. First, we have acitretin and methoxsalen. Soriatane is indicated for treatment of severe psoriasis in adults. Methoxsalen is photochemotherapy, indicated for the symptomatic control of severe recalcitrant disabling psoriasis not adequately responsive to other forms of therapy. When the diagnosis has been supported by biopsy. It is intended to be administered only in conjunction with schedule of controlled doses of long wave ultraviolet radiation.

On the next slide here, we have the dosing and availability. So, acitretin, the initial dose is 25 to 50 mg once daily with a main meal. Again, maintenance dose is 25 to 50 mg orally, and is dependent on the response to the initial treatment. For methoxsalen, initial therapy is one and a half to two hours prior to UVA with low-fat food or milk, based on the drug weight-based dosing table, which is in the TCR. Both of these are available as gelatin capsules. Just to keep in mind, in terms of pediatric, safety and efficacy have not been established in pediatric patients for both of these medications. Acitretin is pregnancy Category X, that is important to keep in mind, whereas, methoxsalen is pregnancy Category C. In terms of renal impairment, acitretin is contraindicated in patients with severely impaired renal function.

Lastly, adverse effects, it is important to keep in mind that acitretin can cause cheilitis over 75% of patients, rhinitis, [inaudible] disorder, pruritus, and dry skin. That all ranges roughly 25 to 50% of patients. Lastly, methoxsalen, adverse events nausea is the most common, roughly 10% of patients, and it's more common with soft gelatin preparations, due to more rapid absorption and increased serum levels. So, that's why taking it with milk or food may help prevent the nausea.

To pivot over to the guidelines, according to the American Academy of Dermatology in 2009, for the guidelines for psoriasis, they note that Soriatane, methotrexate, and cyclosporine have been used for the treatment of psoriasis for many years with good to excellent results. Strength of recommendation was B, level of evidence 2. However, the systemic therapies, Soriatane is the least effective monotherapy. Therefore, it is often used in conjunction with ultraviolet B, UVB, or UVA phototherapy. Soriatane, like the other retinoids, appear to be more efficacious for the inflammatory forms of psoriasis. It has been used as maintenance therapy after 6 to 12 months of continuous treatments, 75 to 88% of patients respectively with chronic plaque psoriasis reached a psoriasis area severity index of 50. It may be combined with tumor necrosis factor inhibitors to augment therapy of negligible of immunosuppressive effects, but due to lack of significant immunosuppression, Soriatane is generally considered the treatment of choice in HIV positive patients with severe psoriasis. Lastly, for UV light therapy, although treatment options for psoriasis have expanded in recent years, UV light therapy remains a therapeutic option for patients. Phototherapy generally lacks the systemic immunosuppressive properties of both traditional and biologic systemic therapies. Soraline [SP] plus PUVA photochemotherapy combines administration of Soraline, a class of phototoxic compound with the exposure to ultraviolet A radiation under strict medical supervision. Lastly, UVA penetrates deeper into the dermis than UVB and does not have UVB's potential for skin burning. The 2010 AAD systemic therapy guidelines for psoriasis was phototherapy and photochemotherapy recommend oral PUVA. Just to note really quickly, published guidelines for management of psoriasis with traditional systemic therapies in 2009 updated their recommendation for management with biologics as part of a consensus guideline. Notably, all

AAD guidelines are given a sunset date of five years following the publication, unless revised. So, while some are undergoing updates, they are not, they have no revised this yet. That's why this is the most current guideline. Updated guidelines for the management of psoriasis and phototherapy, use of nonbiologics, and treatment of pediatric patients are expected later in 2019. I haven't received them yet. Guidelines for the management with topical agents are expected in 2010.

Antipsoriatics topical, so we're not going into background again. We'll move right into indication. So, we have the topical agents for psoriasis, let me see here. We have Dovonex, Sorilux, Calcitrene, calcipotriene solution, Enstilar, Taclonex both ointment and suspension, Vectical, Tazorac, and Duobrii. Again, whether they are available as generic and their respective indications for plaque psoriasis or psoriasis vulgaris, and psoriasis of scalp, and if there are any pediatric indications, you can see them notated in parenthesis both Taclonex ointment and suspension are for greater than or equal to 12 years of age.

Moving on to the next for dosing and availability, as you can see, the dosing and available is stratified. Since this is topical, most of these are ointments or gels or lotions.

For topical guidelines, again moving to the American Academy of Dermatology, traditionally pharmacotherapy choice includes emollients, topical corticosteroids, phototherapy, and systemic medications. Approximately 80% of patients affected with psoriasis have mild to moderate diseases that can be managed with topical agents and emphasizes the importance of tailoring treatment options to meet individual patient needs. Topical corticosteroids remain the cornerstone of treatment for most patients with psoriasis, especially for those with limited disease, and wide availability of strengths and formulations allow the versatility of use. However, limitations exist with topical steroid use. The clinical data available for safety and efficacy of tropical corticosteroid report a short duration of use, approximately two to four weeks, and treatment extending beyond this time period increases the risk of cutaneous adverse effects and systemic absorption. Both systemic and local cutaneous adverse effects are a concern with extensive use of corticosteroids, such as telangiectasia, which is capillary dilation of the

skin surface, striae distensae, acne, folliculitis, and purpura. As a result, despite the corticosteroids being the mainstay of topical treatment, the most potent and efficacious agents are only approved for short-term treatment, approximately two to four weeks. The National Institute of Arthritis and Musculoskeletal and Skin Disease advises the use of topical steroids to help to improve psoriasis but not eliminate the disease. Oftentimes, the affected skin will become resistant to the topical steroid, requiring an alternative agent. Furthermore, rebound exacerbation of the disease has been reported with abrupt discontinuation of the corticosteroid. Therefore, tapering is recommended, but guidance on lacking on details of tapering.

For the National Psoriasis Foundation 2017 Guideline Update, it advises on the treatment of inverse and intertriginous psoriasis, which typically affects skin fold areas, such as the axilla, the perianal skin, the intergluteal cleft, the inframammary genital/inguinal, abdomen, and retroauricular folds. They state that while low potency topical corticosteroids may be appropriate for short-term use, longterm therapy includes topical calcitriol, calcipotriene, and immunomodulators. Antimicrobials, emollients, and coal-tar products are considered second or third-line treatment. For resistant inverse psoriasis, botulinum toxin, laser therapy, and select anti-tumor necrosis factor agents, or anti-interleukin 12/23 treatments are recommended. As I stated earlier, an updated consensus guideline for the care and the management of psoriasis with topicals by the AAD and NPF is expected in the first quarter of 2020.

Lisa Chew: I give Umang to catch his breath. Any questions about the oral or topical antipsoriatics?

Umang Patel: Alright. Let's keep going. So, we have topical immunomodulators. First, a little bit of background. Actinic keratosis, AK, a premalignant condition of the skin that manifests as small thick scaly patches. It is seen mostly in sun-exposed areas of the skin and should be treated due to its potential to progress into squamous cell carcinoma, SCC moving forward. For genital warts, according to the CDC, about 79 million Americans are currently infected with HPV, and 14 million become newly infected each year. Due to its prevalence and likelihood of transmission in sexually

active patients, the CDC encourages vaccination in recommended age groups. Genital warts are typically caused by HPV type 6 or 11 in 90% of occurrences, and they are usually flat papular pedunculated growths on the genital mucosa. No evidence indicates that the presence of genital warts or their treatment is associated with the development of cervical cancer. In terms of treatment, patient applied topical treatments for genital and perianal warts include Imiquimod, podofilox, and sinecatechins. Imiquimod stimulates production of the interferons and other cytokines. Podofilox is a plant-based antimitotic agent. Sinecatechins is a green tea extract that may treat genital and perianal warts via anti-oxidative effects.

Moving here, we see the indication. So, for imiquimod, we have Aldara and Zyclara. For podofilox, we have Condylox, and we have the solution, as well. Then, for sinecatechins, we have Veregen. So, Aldara is indicated clinically typical non-hyperkeratotic, non-hypertrophic actinic keratosis on the face or scalp of immunocompetent adults. It is also indicated for biopsy-confirmed primary superficial basal cell carcinoma in immunocompetent adults. There are parameters on the specific diameter of the said squamous for it. Then, it is also indicated for external genital and perianal condyloma acuminata in patients 12 years of age or older. For Zyclara, it has two indications, clinically typical visible or palpable actinic keratosis of the full face or balding scalp in immunocompetent adults, and external genital and perianal warts, condyloma acuminata in patients 12 years of age or older. Podofilox Solution has indications for treatment of external genital warts and keep a note, it is not indicated in the treatment of perianal or mucous membrane warts. For Veregen, it has indications for the treatment of external genital and perianal warts and immunocompetent patients 18 years of age or older. Safety and efficacy of use beyond 16 weeks, or for multiple treatment courses, has not been established.

In terms of dosing and availability, as you can see, the dosing is based on the indication. The availability, we have creams, gels, solutions, and ointments. So, there is kind of a full gamut of availabilities in this class. Instructions on applications of things like that can be found in the TCR. For contraindications, there are no contraindications listed for imiquimod or sinecatechins. Condylox is contraindicated in patients with

hypersensitivity of any components of the product. There is a note with imiquimod, it's indicated to not use in patients that are... excuse me. Do not use imiquimod cream with sun lamps, tanning beds, or other products that contain imiquimod, as well. Avoid sunlight, if possible. For pregnancy, imiquimod is pregnancy Category C, and no adequate studies for the remaining two. There are no dosage adjustments needed for any products for renal or hepatic impairment.

To pivot over to the guidelines, for actinic keratosis, there are no widely accepted guidelines for the treatment of AK in the United States. The British Association of Dermatologists in 2007 state that the treatment options below are listed, along with their associated strength of recommendation and quality of evidence rating. No therapy is A-II for mild AK. Sun block, SPF-16 or higher, applied twice daily for seven months, is A-I. 5-fluorouracil applied twice daily for six weeks is A-I. Topical diclofenac 3% is B-I. Tretinoin cream and imiquimod 5% cream are B-I as well. For the International League of Dermatological Societies, European Dermatology Forums, for single lesions, they suggest the use of imiquimod 3.75%, or 5%. For multiple lesions, they recommend 3.75% imiquimod, or suggest the use of 2.5 or 5% imiquimod. Now, for genital warts, the CDC's 2015 guidelines recommend these three medications, as patient administered options to treat genital and perianal warts with no preference of one product over the other. Treatment to remove genital wards should be guided by wart size, number, and anatomic site, cost, experience of the healthcare provider, adverse effects, and the preference of the patient. No definitive evidence suggests that any of the available treatments are superior to any other. No single treatment is ideal for all patients or all warts.

So, then we have, the last one we have here is dermatologics, emollients. This one is extremely quick. Just to give you a background for atopic dermatitis, for the third time, a common disease with worldwide prevalence. Clinically eczematous patches and plaques are seen, which favor the face and extensor surfaces in young children in flexor surfaces, including the antecubital and popliteal fossa, ankles, and neck in older children. Management of almost every case of atopic dermatitis will include topical therapy. Patients with mild to moderate eczema, topical therapy may be entirely sufficient to control disease activity, and

emollients should be considered as firstline therapy for mild disease. Patients with more severe disease may require more advanced therapy, including phototherapy or systemic therapy. Other topical therapeutic options for more advanced cases of atopic dermatitis include corticosteroids and calcineurin inhibitors. For xerosis or dry skin, it's caused by loss of water in the upper layer of the skin. Emollients work by forming an oily layer over the top of that skin that traps water in there. These agents are designed to make the stratum corneum softer and more pliant by increasing its hydration. A large number of preparations are available, many of which are marked as cosmetic and therapeutic moisturizers.

In terms of place of therapy, emollients may be applied multiple times daily, and especially after bathing. Continued use of emollients during periods of disease quiescence can reduce the tendency of eczema flares. Studies have shown that moisturizers lessen symptoms and signs of atopic dermatitis, including pruritus, erythema, fissuring, and lichenification, thus resulting in some reduction in inflammation in atopic dermatitis severity. In a study 52 children with eczema treated with medium potency topical steroid to lesional skin for two weeks, subsequent daily application of emollient significantly improved xerosis and pruritus compared to no application of emollient. Patients are generally instructed to emollients liberally, though the clinical meaning of this term is subjective. In study of 67 pediatric patients, 48 with eczema and 19 control, found that 130 g/m2 per week of emollient was adequate for 95.8% of patients. However, this study did not detect difference in clinical response.

On the next slide, so something to notice is we have posted the TCR for this on the web portal for the, for the committee. There are 16 pages of tables of dosing and availability and things like that. So, buckle in. We're not going through page by page. That's all for your... that's only for you guys if you would like to go over it, but that, that is the end of emollients there. Then after this, just as I mentioned earlier with HIV, the appendices are here. That's where all the HIV dosing and availability charts are.

Lisa Chew: Thank you. Umang deserves a gold medal today. Again, no stakeholders.

Donna Sullivan: I am going to bring up a couple files. Okay. Maybe I won't. So, I was going to show you the classes here that are the dermatologics that are preferred. So, for the psoriatics oral, the Acitretin is preferred, the calcipotriene is preferred topicals. Then, the [inaudible], eladil, and pimecrolimus is the preferred topical agents there. Then, in our emollients class, we are preferring a urea cream. Then, we classify... Umang had mentioned some of the drugs for the perianal warts. We have them in a different drug class name, but we have the podofilox as preferred, as well as some topical salicylic acid preparations. So, with emollients, again, it's the lactic acid creams, hyaluronic gel, the urea 40%, and then some vitamin A and D ointment combinations. Then the podofilox, like I mentioned, and the salicylic acid topical products that are generic. Our keratolytic and antimitotic agents and the emollients will not actually be implemented until April of 2020. So, you won't see them listed on our online PDL yet. So, these are the drug classes that we are discussing right now. Again, our standard kind of recommendation, all products are considered safe and efficacious and eligible to be preferred, and grandfathering is at the discretion... preferred status and grandfathering is at the discretion of Health Care Authority with a trial of two preferred products with the same indication before a nonpreferred drug would be indicated, unless there is contraindications or clinical reasons for using the nonpreferred first, or, of course, if there is only one preferred product in the class. So, the motion.

Lisa Chew: So, the keratolytic and the mitotic agents, we didn't cover today? Should that be taken off the...

Donna Sullivan: I believe we did cover them today. It's just we... he calls... our drug class names differ from the Magellan drug class names. So, they were included. Is that correct?

Umang Patel: Yes. They were.

Donna Sullivan: Yes.

Susan Flatebo: I move that all products in the dermatologics drug class, as listed on slide 21, are considered safe and efficacious and are eligible for preferred

status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of 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.

Catherine Brown: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries. So, do you want to make any comments about the opioid?

Donna Sullivan: I can just really quick. So, the Support Act... Okay. So, we're making changes to our opioid policy. So, we'll quickly go through why we're making the changes. So, we'll go over what is changing, our current policy, how we're actually making the changes, and then future requirements of the support act. So, why are we doing this? The Support Act was passed in October of 2018. It directs many federal agencies, including the Medicaid program to make some changes.

So, the full name is the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act, or Support for the Patients and Communities Act, and it required Medicaid, as well as Medicare and all of these other agencies listed to make changes.

So, what is actually changing in the Support Act? So, January of 2019, for Medicare, there was a care coordination edit required for all Medicare Part D Plans that went into effect at 90 MED, or mg-equivalent doses. Then they also had a hard stop at 200 MED that was optional. They also required a soft edit for concurrent prescribing of opioids and benzodiazepines, as well as duplicate longacting opioid therapy and acute therapy or first prescriptions. They had a hard edit that it couldn't be for more than a seven-day supply. So, earlier this year, there was a lot of confusion, thinking that the Medicaid program had implemented these

changes, but actually, we were not required to make changes until October of 2019, and we have actually delayed implementation to November of 2019 so that we can make sure that get everything programmed accordingly and try to minimize any disruption. So, what we were required to do is a maximum daily dose or MME limit, again safety edits for subsequent opioid prescriptions, monitoring concurrent use of opioids and benzodiazepines, opioids and antipsychotics, and antipsychotic use in pediatric patients.

Also, there are requirements that are to the PDMP monitoring program that are in the future. So, what our current policy is, is we have a short-acting opioids are limited to 42 tablets for individuals greater than or equal to 21 years of age, and 18 tablets for those that are less than or equal to 20. Then, we have exceptions for patients that have serious medical conditions and that require higher quantities. So, this is for an acute prescription. Somebody, they break their leg. They have a surgery. The provider can write exempt on the prescription. Then, the pharmacy has a code that they can submit the claim with, and the claim will process. There is also a separate code for active cancer treatment. So, if a patient has active cancer pain, is in end of life care, is in hospice care, or palliative care, if the physician indicates that on the prescription when they write the prescription, the pharmacist can then use a different code to get the claim to process without having to get a prior authorization requested. Typically for longacting opioids, we don't authorize those for an acute prescription. So, any longacting opioid would not be authorized unless there is really a good clinical reason why they have to start off using a longacting version of the medication, rather than a short-acting opioid. Then, our acute use policy is limited to 42 days in a 90-day period. So, if you want to use more than 42 days of opioid therapy, we have a process for getting authorization.

For our chronic use policy, so beyond the 6 weeks or 42 days, the provider will have to submit an attestation form, basically attesting that they're following best practices so that there is an ongoing clinical need. The patient is on non-opioid treatment. They are looking at baseline and ongoing assessments of pain and function. They are screening for other mental health disorders. They are getting periodic urine drug screens. They're checking the PDMP for other opioids that the patient might be

taking. I think real importantly, they're discussing realistic goals with the patient of what to expect on opioid therapy, meaning that, you know, the expectation might not be that you're going to be pain free. It'll be tolerable pain and if they are improving function or pain status, then possible even consider discontinuing the opioid altogether. The patient must accept the conditions, and we request that they have a signed pain contract or informed consent of some sort.

So, that is really just the provider is checking the boxes and signing the form and kind of attesting that they're following those processes. We don't go back and check chart notes to double check to see if they actually are. So, what's changing for November is, we're implementing a morphine milligram equivalent dose of 120 MME per day. That is going to be regardless of diagnosis. So, that code that overrides the 42 tablets or 18 tablets for active cancer patient or the exempt codes won't be allowed for exceeding the 120 MME daily dose. So, prescriptions exceeding 120 MME but are still less than 200 MME will require prior authorization through the attestation process. So, we're amending our form to include a high dose attestation, in addition to the chronic use attestation. Then, prescriptions that exceed 200 mg per day will be considered on a case-by-case basis. We are identifying patients that are currently exceeding 200 MME, and we are going to place an authorization for those patients for 12 months. Then, after that 12-month period, they will need to go through the attestation process. The provider will have to verify that they are following best practices.

So, the high dose attestation, again, it will be authorized, and these are the practices that are on the form. The provider will attest that either the patient is currently on a chronic opioid regimen and that they need to temporarily escalate to a dose above 120 MME, but no more than 200 for a short period of time. So, less than 42 days. Or that they're following a taper plan. So, they're on a high dose above 120, but they are tapering down, and they need to be allowed to continue to be above 120, but they are coming down. There needs to be a documented medical need of why they need 120 per day or more than 120 per day.

This is kind of small. I apologize. Our guidelines also kind of mirror the rules that were changed for all of the medical commissions earlier, I think

it was last year. So, the provider... to exceed 120 MME that was the threshold that was agreed upon by all the medical commissions. In order to exceed it, the recommendation is that they get a consultation with a pain specialist, either through an office visit, a telephone consultation, or an audio-visual interchange between the two providers. Or, the provider, if they're a board certified pain specialist, they just need to let us know that they are board certified. Or, if they have completed the 12 hours of continued education, we'll approve the 120 MME without a consultation. Or, if they're a provider working in a pain management clinic, they don't need to have the consultation. Or, if they have a minimum of three years clinical experience in pain management setting, or the patient requires 120 MME for active cancer pain, in those circumstances the provider doesn't need to get a consultation. We will just go ahead and approve the attestation if they check that particular box.

For over 200 MME per day, it'll be a prior authorization. We will require both to complete an attestation form and also chart notes to be submitted, justifying the need to exceed the 200 MME. It should include the consult specific to the requested dose, unless one of those other exceptions apply, and we'll just be looking for those chart notes to make sure that they actually have a medical need documented in their records. We're not going to judge potentially the need, unless it's clear that they don't have a reason to be on an opioid at that particular dose.

So, just some items to note. The new MME limit is in addition to the acute pill limit. So, short-acting opioids are still going to be limited to the 42 tablets for the 21 and older, and 18 tablets for 20 and younger, but if those 42 tablets exceeds a 120 MME, then they'll have to go through that high dose attestation. So, it's whichever is less. So, there are certain strengths of certain short-acting opioids that would exceed 120 MME getting 42 tablets. I'm thinking, like, the hydromorphone potentially. The chronic use, like I said earlier, we'll still have one attestation form with two pieces in it. So, there is the possibility that you can submit the chronic use attestation form. Then, if you exceed that 42 days of treatment, you will have to resubmit the form for the chronic use section. We won't be accepting an attestation for chronic use before a patient has been an opioid for at least 35 days. We have experience where patients are being prescribed their first opioid prescription, and they're giving a

chronic attestation at the same time. So, we don't understand... we're not going to allow you to predecide that you're going to be able to... you're going to have chronic treatment until it's determined that it's actually medically necessary. Then, opioids that are prescribed pursuant to an emergency department visit will be granted an exception. So, if the pharmacy has a prescription with an ED from an emergency department, they can call and get an override for the greater than 120 MME without submitting an attestation. We don't want to put a huge barrier in front of patients that are coming out of an Emergency Room with an acute need for a prescription before they can get in to see their primary care provider.

Then, future changes is that beginning October 1st of 2021, the Support Act requires the Medicaid agencies to have criteria in place for the providers to check the PDMP prior to writing a prescription for all controlled substances. So, we are working with the Department of Health who administers the prescription drug monitoring program to try to coordinate how we're going to make that happen. More information on that particular process will be available in 2021. That is it. Before we adjourn, we have to go back and make motions on the first two drug classes from this morning. So, I apologize. We missed those. The PCSK9 inhibitors and the...

Nancy Lee: A question slightly related to the opioid, some hospitals are transitioning to ERX for controlled substances. Have you had experience with some of that yet with your Medicaid patients? I don't know if that's created any kind of hindrance or barrier to any process.

Donna Sullivan: I don't know if that does or not. I'm not sure what that looks like from a... we know that electronic transmission of controlled substances is happening. Whether or not that's... I don't think that bypasses our edits any, because that transmission is from the provider to the pharmacy. The pharmacy still has to transmit the prescription to us. So, it shouldn't have any impact on that.

Christopher Chen: Just a couple of questions about the Support Act. One, patients that are obviously on high doses of opioids are also the most susceptible to

withdrawal. Is there some sort of process for a warning before that year attestation expires or some grace period built in?

Donna Sullivan: So, the one year authorization kind of is their grace period. They don't have... we're not requiring them to taper down. We're just requiring that they get that form filled out.

Christopher Chen: They have to fill that out every year.

Donna Sullivan: And I believe, right now, we do have is it seven days? I'll look to Amy and Dave, like, for somebody with a 120, if they hit the 120, require the attestation immediately, I forget. Did we say we'd give them a one-time fill or a short supply while the doctor is notified and gets the form filled out? I forget exactly what we landed on there?

Petra Eichelsdoerfer: There is an authorization for an emergency fill that would cover for emergencies of any kind, basically.

Christopher Chen: I am just kind of thinking out loud here. I'm trying to reconcile the time limits on the acute opioids with the chronic... so acute use is limited to 42 days in a 90 day period.

Donna Sullivan: Correct.

Christopher Chen: Then, chronic, you need to have at least 35 days of opioid use. Does that mean that if you need acute opioids for more than 42 days in your first three months, then you're automatically going onto chronic?

Donna Sullivan: So, what that basically means is that after 40... so, we allow a 42 day supply in a 90-day period. If you are thinking that you need to go beyond 42 days of treatment, you can submit a chronic use opioid attestation form after 35 days have passed where the patient has been on treatment. Does that answer your question? Then, we would consider you to be a chronic opioid user after you have reached 42 days supply.

Christopher Chen: Okay. Yeah. I think that was my question. So, after 42 days, you have become chronic?

Donna Sullivan: Correct.

Lisa Chew: Would it be possible to get electronic copy of these slides sent to us?

Donna Sullivan: Yes.

Lisa Chew: Okay. Great. Thank you.

Petra Eichelsdoerfer: They're actually on the Health Care Authority opioid website.

Leta Evaskus: I have also put this on the Washington Prescription Drug Program website under meetings and materials.

Donna Sullivan: So, any other questions on that? So, going back to the PCSK9 inhibitors, we just need a motion, standard recommendation. I'm not going to read it. There are, I believe, two PCSK9 inhibitors on the market at this point in time. We have one of them preferred.

Constance Huynh: I move that all products in the antihyperlipidemics PCSK9 inhibitor drug class are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of Health Care Authority. All nonpreferred products require a trial of two preferred products with the same indication before a nonpreferred drug would be authorized, unless contraindicated, not clinically appropriate, or only one product is preferred.

Virginia Buccola: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? And the motion carries.

Donna Sullivan: Then, the next class is the ADHD narcolepsy class, so both the stimulants and the nonstimulants. This should be slide 3. Actually, yes, slide 3.

Jordan Storhaug: I move that all products in the ADHD narcolepsy drug classes listed on slide 3 are considered safe and efficacious and are eligible for preferred status and grandfathering at the discretion of the Health Care Authority. All nonpreferred products require a trial of 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.

Constance Huynh: I second.

Lisa Chew: All those in favor, say aye.

Group: Aye.

Lisa Chew: Any opposed? Okay. The motion carries. Did we miss any other? Is that it?

Donna Sullivan: I believe we are finished.

Lisa Chew: Okay. We are adjourned. Thanks everyone.

Donna Sullivan: Thanks very much.